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(From the Pediatric University Clinic, the Children's Hospital, Gothenburg (Head: Professor YNGVE ÅKERRÉN, M.D.), and from the Elementary Schools of Gothenburg (Head Medical Officer: Dr. E. GEDDA)

The Prognosis of Bronchitis Asthmatoides during the First Year of Life

by KJELL L. MÖLLER

A physician with a clientele of children does not seldom come across infants with symptoms which resemble or are identical with those of asthma or asthmatic bronchitis seen in later years. The infant coughs, has obvious expiratory dyspnoea and, if it does not cry at examination, ample sibilant rhonchi are heard diffusely over the lungs during expiration. Sometimes the patient has fever and signs of upper respiratory infection, sometimes not. An acute, diffuse bronchitis involves the secretion of viscous mucus and pronounced swelling of the mucous membrane to such an extent that a relative stenosis in the fine bronchi is present. Moreover, the bronchi are narrower on expiration than on inspiration, which explains the expiratory dyspnoea and other physical findings. The physician mentions spasm in the bronchi, speaks of allergy, and perhaps makes the diagnosis of asthma or asthmatic bronchitis which may "grow away" or possibly have a worse prognosis. The parents, perhaps having had experience with asthma, look towards a dismal future and might be more pessimistic than is necessary. What is the prognosis for infants with this clinical picture? Is there a great risk that an invalidizing asthma will develop? To try to elucidate these questions, this investigation has been performed.

Earlier Investigations

Diagnosis.—Certain authors are of the opinion that bronchial asthma is a very rare illness during the age of infancy, if it occurs at all (FINKELSTEIN). Others, probably the majority, believe that asthma may very well develop during the first year of life (cf. BROCK, BUFFUM). BRAY mentions that of 1,390 cases of asthma during childhood 22.25 per cent started before the age of one year. It is impossible distinctly to define the diagnoses bronchial asthma and asthmatic bronchitis (spasmodic bronchitis) of different types in the infant (BAAGOE). RATNER, among others, points out that many illnesses in the infant may cause an asthma picture. He also believes that a definite diagnosis of asthma should not be made on the basis of an isolated

attack of dyspnoea followed by sibilant rhonchi. Only with repeated attacks, and especially if they are preceded or followed by eczema, urticaria or recurrent upper respiratory infections, is the suspicion of asthma justified. He calls the attention to Chevalier Jackson's aphorism: "All is not asthma that wheezes."

Prognosis.—The prognosis is judged differently, but has generally been considered good. Some cases heal spontaneously during puberty (MONRAD). SUFFUM has observed 265 cases of asthma during childhood, 32 per cent of which started during the two first years of life, and these children had a worse prognosis than children becoming ill later on. WAJSMAN distinguishes between asthma in infants and young children, who have a tendency of recovering during the age of puberty, while older children have a worse prognosis. BROCK has studied the histories of 351 asthmatic children. The usual time of onset was 2–4 years of age, but not unusual during the first year of life. Improvement occurred in all ages, but this tendency increased strongly after the age of 10 years, and culminated during the age of puberty, when 33 per cent were free of asthma. The total time of illness lasted 8–10 years for $^2/_3$ of the children who recovered. FLENSBORG has followed-up 298 children treated for bronchial asthma at children's hospitals in Copenhagen. The illness started before the age of 5 years in most of the cases, and in 20, during the first year of life. Of the 131 patients who, at the follow-up examination, were 18 years of age, 41.1 per cent had no attacks of asthma. The boys were mostly free from symptoms at the age of 12–15 years, and the girls at the age of 9–12 years. BOESEN has tried to find out if an asthmatic bronchitis precedes a true bronchial asthma or not. In 1951, questionnaires were sent to 166 children who had been treated for asthmatic bronchitis at the children's hospitals in Copenhagen from 1940 to 1945. Of the 85 infants included in the case-material and who, at the follow-up study, had reached the mean age of 8.3 years, 6 per cent had asthma.

The frequency of asthma among children differs slightly in the literature. KRAEPELIEN (also personal information) has, as regards Sweden, by the guidance of information from the Board of Education during the sessions 1948/49 and 1949/50, estimated the asthma frequency at 0.78–0.81 per cent for 7–10 year old children, and 0.53 per cent for children aged 13–14 years. After a direct inquiry with the school physicians in Stockholm in 1953, the figures there were 1.61–1.42 per cent for 7–10 year old children and 0.87 per cent for children aged 14 years. During 1948/49 the County of Gothenburg and Bohus reported asthma among 7 year old children, in 1.89 per cent; among children aged 10–12, in 0.68 per cent; and aged 13–14, in 0.62 per cent. He points out that in the official reports given by the school physician, the frequency of asthma varies according to what one doctor or other classifies as asthma. To distinguish between bronchial asthma and asthmatic bronchitis is furthermore difficult, as both diagnoses intermingle. The cases which are subjected to official reports probably have more obvious symptoms and a larger proportion probably have true bronchial asthma.

In Copenhagen about 1 per cent of the school-children have asthma (cf. BOESEN).

As regards Norway, EILERTSEN has found asthma and asthmatic bronchitis in 1.77 per cent among children in the first years at school.

A distinct *difference in sex* can be found regarding the childhood asthma. FLENSBORG has found that 64 per cent are boys and 36 per cent girls. BOESEN and WALTHER have arrived at approximately the same figures.

An *allergic heredity* can be stated in the majority of children with asthma, e.g. according to WALTHER, in 70 per cent. Among BOESEN's 24 infants with uncompli-

ter ("pure") asthmatic bronchitis there was allergic heredity in 33 per cent, and 12 per cent of these infants later developed asthma.

It is unchallenged that *eczema*, in many cases, precedes asthma during childhood. Of the asthmatic children examined by BROCK, more than half had previously had eczema. In these children, the onset of asthma was earlier, but the symptoms were not worse than in those without eczema. BOESEN's case material does not allow conclusions regarding the prognostic importance of eczema.

According to BOESEN, *eosinophilia* seems to impair the prognosis, but neither in this respect is it possible to make sure conclusions from his material.

Case Material and Methods

The investigation includes children, born between 1934 and 1946, and who during the first year of life were hospitalized at the Children's Hospital of Gothenburg for bronchial asthma, bronchitis asthmatica or bronchitis asthmatoides. They amount to 177. All records of infants from the same period of time, diagnosed as bronchitis with or without suffix, have furthermore been studied. From the case histories it was obvious in some of these cases that there had been a condition resembling asthma, i.e. an expiratory dyspnoea and diffuse sibilant rhonchi during expiration. The number of infants in this group was 56. In quite typical cases of bronchiolitis expiratory dyspnoea sometimes occurs, and on physical examination prolonged expiration is found. Cases diagnosed as bronchiolitis have not been included in this investigation. The custom of making an asthma diagnosis has obviously changed in the course of the years. During certain periods all children with the symptoms described above have been diagnosed as having asthma. But in other years only 70–80 per cent of the children with identical symptoms were given the diagnosis asthma. To motivate the diagnosis of asthma a statement as to an allergic heredity, eczema and/or blood eosinophilia has been required during certain years, as seen in the table below:

Diagnosis in the records	Number of cases	Eczema %	Heredity %	Eosinophilia %
Bronchitis asthmatica etc.	177	22.0±3.1	39.0±3.7	38.8±3.9
Bronchitis ac. etc.	56	24.8±4.7	6.6±5.0	11.6±6.3
Difference:		7.2±5.6	22.4±6.2	27.2±6 3

The total number of infants treated in the hospital with asthmatic symptoms will thus amount to 177 + 56 = 233. Of these 154 (66.1 per cent) were boys and 79 (33.9 per cent) girls, a sex distribution which is prevalent in case materials of asthma during childhood.

Naturally this case material is selected. For one thing, only the children who are seriously ill are hospitalized, i.e., with the most pronounced asthmatic picture, alarming dyspnoea etc. Secondly, the children are mainly admitted who come from the worst social milieu; thus, if the dwelling is small, cold, draughty, and damp, or if the mother is alone, tired-out or otherwise incapable of caring for her child at home. Of the 233 children, 184 are from the lowest social class. Therefore, it is important

to note that the case material is likely to include asthmatic infants with, from the prognostic point of view, the most unfavourable prospects.

So far as is known, three of the children died later from diseases which had no connection with asthma.

In the spring of 1954 I tried to get in touch with the guardians of the remaining 230 children and managed to establish personal contact in 109 cases. The remaining 121 have been sent a questionnaire regarding the history of the child and his present state of health. No reply was given in 11 cases. The follow-up examination thus includes 219 children of originally 230, or 95.6 per cent.

In order to get an opinion of the approximate frequency of asthma, asthmatic bronchitis or recurring bronchitis of children attending school, I have estimated this in one of the Elementary School districts in Gothenburg. During the autumn of 1953 and 1954 I personally questioned the guardians of the children in the first class (aged 7 years) and second class (aged 8 years). Data about children in the 4th class (aged 10 years) and 8th class (aged 14 years) have been found in the school records, and also by questioning the teachers and the children themselves.

Results

It was impossible at the follow-up study sharply to distinguish between the diagnoses of bronchial asthma and asthmatic bronchitis, as well as bronchitis asthmatica and bronchitis acuta recidivans or bronchitis chronica. In the following, I have considered children to suffer from asthma who have shown obvious attacks of dyspnoea, been considerably invalidized owing to their illness and who, in most cases, have been diagnosed and treated by an allergist. Other children with bronchial trouble have been characterized as suffering from bronchitis only. When a child has been free of symptoms for 1 $^1/_2$ years, only then has it been regarded as healthy.

The time of observation at the follow-up study in Spring, 1954, was between 7 and 20 years and for 50 per cent of the children it was 12 years or more.

The following compilation shows the number of boys and girls respectively (in per cent) with asthma and bronchitis in 1954. The entire morbidity of the case material is shown in percentage also.

	M	F	M + F
Asthma	6.3 ± 2.0	4.0 ± 2.3	5.5 ± 1.6
Bronchitis	16.7 ± 2.9	13.3 ± 3.9	15.5 ± 2.5
Asthma + bronchitis			21.0 ± 2.8

No sure difference in sex could be stated.

Of the 93 children born 1934–1941 (> 13 years), 16 or 17.2 ± 3.9 per cent suffered from respiratory trouble, against 30 or 23.8 ± 3.8 per cent of

TABLE 1

The frequency of asthma and bronchitis, respectively, among children in Gothenburg attending Elementary Schools.

	No. of cases with asthma			No. of cases with bronchitis			Cases with asthma + bronchitis
	M	F	M + F %	M	F	M + F %	M + F %
1st class: aged 7 Number: 749	14	1	2.0 ± 0.5	13	15	3.7 ± 0.7	5.7 + 0.8
2nd class: aged 8 Number: 466	7	0	1.5 + 0.5	5	7	2.6 ± 0.8	4.0 ± 0.9
4th class: aged 10 Number: 342	1	1	0.6 ± 0.5	1	4	1.5 ± 0.6	2.1 ± 0.7
8th class: aged 14 Number: 112	1	0	0.9 ± 0.9	0	1	0.9 ± 0.9	1.8 ± 1.3
Total: 1669	23	2	1.5 ± 0.3	19	27	2.8 ± 0.4	4.3 ± 0.5

the 126 born later on. The difference is not statistically significant. However, when studying the child during the year that it definitely became free from respiratory symptoms, there is a tendency for the symptoms to disappear as the child grows older.

Skin changes which have been so pronounced that the diagnosis of *eczema* was made during the child's hospitalization occurred in 46 cases, or 21 per cent. The relative frequency of the diagnosis of eczema has not varied remarkably over the years (nor has any variation in years been observed regarding the factors eosinophilia and allergic heredity, dealt with below).

At follow-up examination 13, or 28.3 ± 6.6 per cent, of the children with eczema had respiratory trouble, 6 or 13.4 ± 5.0 per cent of which had asthma. The remaining 173 children without any eczema had respiratory trouble in 19.1 ± 1.0 per cent, 3.5 ± 1.4 per cent of which had asthma. The differences are not statistically significant.

There is no significant difference in the percentage of respiratory trouble children with *allergic heredity*.

The same applies to children with *eosinophilia*. Eosinophile counts were made in 186 children during their hospitalization. An eosinophilia (= 400 eosinophilic cells per mm^2) occurred in 34.4 per cent of these. Of 46 children with eczema, 30 had eosinophilia.

If the children who have shown *neither eczema, allergic heredity nor eosinophilia*, are compiled in one group there will be 88 cases. In this group

no child had asthma at follow-up study, but respiratory trouble occurred in 18.2 ± 3.8 per cent. Compared with the 131 remaining children, suffering from asthma in 9.2 ± 2.4 per cent, there will be a significant difference of 9.2 ± 2.6 per cent.

The infants treated at the Children's Hospital before the age of six months (133 cases), do not show any significant difference in the frequency of respiratory trouble later on compared with those who were older than six months during hospitalization.

Table 1 shows the frequency of *asthma and bronchitis* which I have found in *one Gothenburg's Elementary School districts.*

The percentage of children with asthma tallies rather well with KRAEPELIEN's figures.

A comparison has been made between children in the hospital case material, who were born during 1939–1946, and children in the school case material:

	Number	Asthma %	Bronchitis %	Asthma + Bronchitis %
Hospitalized children . . .	179	3.9 ± 1.4	19.0 ± 2.9	22.9 ± 3.2
School-children	1669	1.5 ± 0.3	2.8 ± 0.4	4.3 ± 0.5
Difference:		2.4 ± 1.5	16.2 ± 3.0	18.6 ± 3.2

There is a predominance of younger children in the school material. The differences found are therefore not quite adequate.

Conclusions and Discussion

Of the 219 children who were hospitalized during infancy for asthmatoid bronchitis at the Children's Hospital of Gothenburg, there were 5.5 per cent who at the follow-up study had asthma and an additional 15.5 per cent had bronchitis of various types (the time of observation 7–20 years and ≥ 12 years for about half). No significant difference between the sexes could be stated from the prognostic point of view. There is a tendency to recover as the patient grows older. The case material does not prove that later on children with only eczema, eosinophilia, or allergic heredity will have a greater tendency to respiratory diseases. If, however, all children with one or more of these factors are compiled to one group, an increased frequency of asthma can be seen in these children. A comparison between the occurrence of asthma and bronchitis in schoolchildren in Gothenburg does not give any significant difference regarding asthma, but instead the hospital case material shows an excess of bronchitis.

As has earlier been pointed out, the reported hospital case material must include those children who, from the prognostic point of view, are most unfortunate. Despite this, the risk of an invalidizing asthma during the years at school or soon after will not be very great. An infant with a bronchitis resembling asthma, who has no massive allergic heredity and/or eczema, may have a good prognosis as regards asthma. That an acute bronchitis in an infant gives a clinical picture resembling asthma may be explained by the anatomic-physiologic conditions which are prevailing at this age.

Summary

At the Children's Hospital of Gothenburg, 219 infants with so-called asthmatoid bronchitis have been hospitalized between 1934 and 1946. They were followed up in the spring of 1954. It has been pointed out that the children with the most severe prognosis were admitted to the hospital. At the time of follow-up examination, 5.5 per cent of the children had asthma and 15.5 per cent, bronchitis. Thus, 79 per cent had no symptoms at all. A tendency of recovery could be seen in older ages. The asthmatoid bronchitis during the first year of life was, for most of the cases, the only attack of illness. The risk of contracting asthma was greater for the group of infants who had eczema, eosinophilia and/or allergic heredity. Case material of children attending elementary schools in Gothenburg showed asthma in 1.5 per cent and bronchitis in 2.8 per cent. Compared with the school-children, a group of children followed up of about the same age, showed no significant increase in the frequency of asthma, but rather an excess of bronchitis. An infant having asthmatoid bronchitis, but no other allergic manifestations or allergic heredity, has a good prognosis with respect to asthma.

Pronostic de la bronchite asthmatique dans la première année de la vie.

219 nourrissons, admis à l'Hôpital des Enfants de Gothemburg de 1934 à 1946 pour bronchite asthmatique, ont été suivis jusqu'en 1954. On a noté dans les cas suivis 5,5 % d'asthme, et 15,5 % de bronchite. 79 % ne présentaient plus aucun symptome. Le risque de voir se développer un asthme a été plus important dans le groupe d'enfants présentant de l'eczéma, de l'éosinophilie, ainsi que (ou bien) des antécédents familiaux d'allergie. Par comparaison avec un groupe d'enfants fréquentant les écoles primaires, et chez lequel on trouvait asthme dans 1,5 % et bronchite dans 2,8 % des cas, les enfants suivis, au même âge, ne présentaient pas plus souvent d'asthme, mais seulement de bronchite. La conclusion à tirer est qu'un nourrisson qui manifeste une bronchite asthmatique, sans autres localisations allergiques, ou sans hérédité allergique, a un bon pronostic quant aux possibilités de voir se développer un asthme.

Die Prognose der asthmatoiden Bronchitis während des ersten Lebensjahres.

219 Säuglinge, welche 1934–1946 wegen asthmatoider Bronchitis im Kinderkrankenhaus Gothenburg stationär behandelt wurden, wurden 1954 nachuntersucht. Die Katamnese ergab, dass 5,5 % der Kinder Asthma und 15,5 % Bronchitis hatten, während 79 % symptomfrei waren. Das Risiko einer Asthmamanifestation war bei jener Gruppe von Kindern grösser, welche Ekzem, Eosinophilie und/oder eine erbliche

allergische Belastung hatten. Eine Serie von Volksschulkindern zeigte bei 1,5 % Asthma und bei 2,8 % Bronchitis, die nachuntersuchten Kinder der gleichen Altersgruppe wiesen keine grössere Häufigkeit von Asthma, dagegen aber häufiger Bronchitis auf. Es wird der Schluss gezogen, dass ein Kind mit asthmatoider Bronchitis, aber ohne andere allergische Manifestationen oder erbliche allergische Belastung, in Beziehung auf Asthma eine gute Prognose hat.

Pronóstico de la bronquitis asmatiforme durante el primer año de vida.

219 niños, hospitalizados en el Hospital de Niños de Gotemburgo (1934–46) por bronquitis asmatiforme, fueron controlados en 1954. En este examen se encontró que 5,5 % sufría de asma; 15,5 % de bronquitis mientras que el 79 % no presentaba ningún síntoma. El riesgo de contraer asma fué mayor en el grupo de niños que habían tenido eczema, eosinofilia y/o herencia alérgica. En series de niños que concurren a las escuelas elementales, se encontró que el 1,5 % sufren de asma y el 2,8 % de bronquitis. Los niños estudiados, de la misma edad, no presentaban mayor incidencia de asma pero sí de bronquitis. Se concluye que un niño con bronquitis asmatiforme pero sin otra manifestación o herencia alérgica tiene un buen pronóstico en cuanto a asma se refiere.

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From the Swedish Public Health Institute, Dept. of Public Hygiene, Tomteboda, and the Sachs' Hospital for Children, Stockholm

Ultraviolet Air Disinfection in a Children's Hospital

A Technical and Bacteriological Study[1]

by GUNNAR LAURELL and HANS RONGE

Air disinfection with ultraviolet irradiation is one of the best-tested methods for the prevention of airborne infections. It has been used, for example, in barracks, schools, assembly rooms, offices and hospitals. Surveys of the comprehensive literature on the subject have been published in recent years, and reference is made to them for detailed information (PERKINS *et al.* 1947, BOURDILLON *et al.* 1948, RONGE 1948, LANGMUIR *et al.* 1950, CRUICKSHANK *et al.* 1954). To sum up, it must, however, be stated that the original high expectations have not been entirely fulfilled. The clinical value of air disinfection is now a debated question, although it is still generally considered that, under certain conditions, ultraviolet irradiation may contribute to reducing the incidence of nosocomial infections. The best results are obtained in institutions in which it is possible to control other modes of infection than the airborne alone. Such possibilities are afforded by children's hospitals, particularly by departments for infants and prematures. In some previous investigations,ultraviolet irradiation has, in fact, been found effective in children's hospitals (ROSENSTERN 1948). A prerequisite for obtaining good results with ultraviolet irradiation is, however, that the installation be planned and executed technically in such a way that it is really effective.

The present paper is an account of the experience gained in connexion with the installation and use of ultraviolet irradiation equipment at the Sachs' Hospital for Children, Stockholm. The investigation period covered January, 1951, to December, 1953.

Planning of the Investigation

The object of the investigation was to produce an installation with the highest possible bactericidal effect without risk of radiation injury to

The investigations have been supported by grants from the Swedish Technical Research Council and the Swedish Medical Research Council.

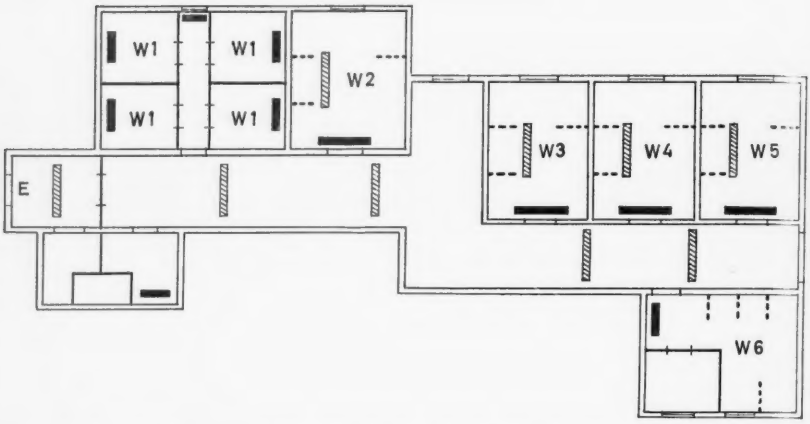

Fig. 1. Plan of the department for prematures, showing the placing of the fittings for ultraviolet irradiation. E = entrance. W_1–W_5 = ward units. W_6 = room for breast-feeding. Black rectangle denotes fitting for upper air irradiation, and shaded rectangle, fitting for curtain irradiation.

patients and staff. For this reason, special lamp fittings and suitable apparatus for radiation measurements were constructed. The bactericidal effect was studied mainly on bacteria sprayed in the air. Altogether about 50 experimental series were made, each comprising from 5 to 10 successive bacterial counts in the air. In the control series, the die-away rates in the air were measured with the lamps turned off, and in the experimental series these rates were measured with the lamps turned on. In many cases, an additional series was made with the lamps on and a fan for increased circulation of the air in the room. Also performed were 27 experimental series for determination of the normal bacterial content of the air in irradiated and in unirradiated rooms.

Methods

Hospital

The investigations were carried out at the new Sachs' Hospital for Children, which was opened in January, 1950. The department for premature infants, in which the investigations were performed, is equipped with ultraviolet lamps for air disinfection throughout. The principles on which it is planned are seen in Fig. 1, which also shows the placing of the ultraviolet lamps. The lamps are turned on throughout the 24 hours.

The department contains 20 beds distributed over 5 rooms. Room 1 contains 4 entirely enclosed cubicles separated by a central passage. The smallest prematures are placed in this room on admission, and the somewhat larger prematures in Room

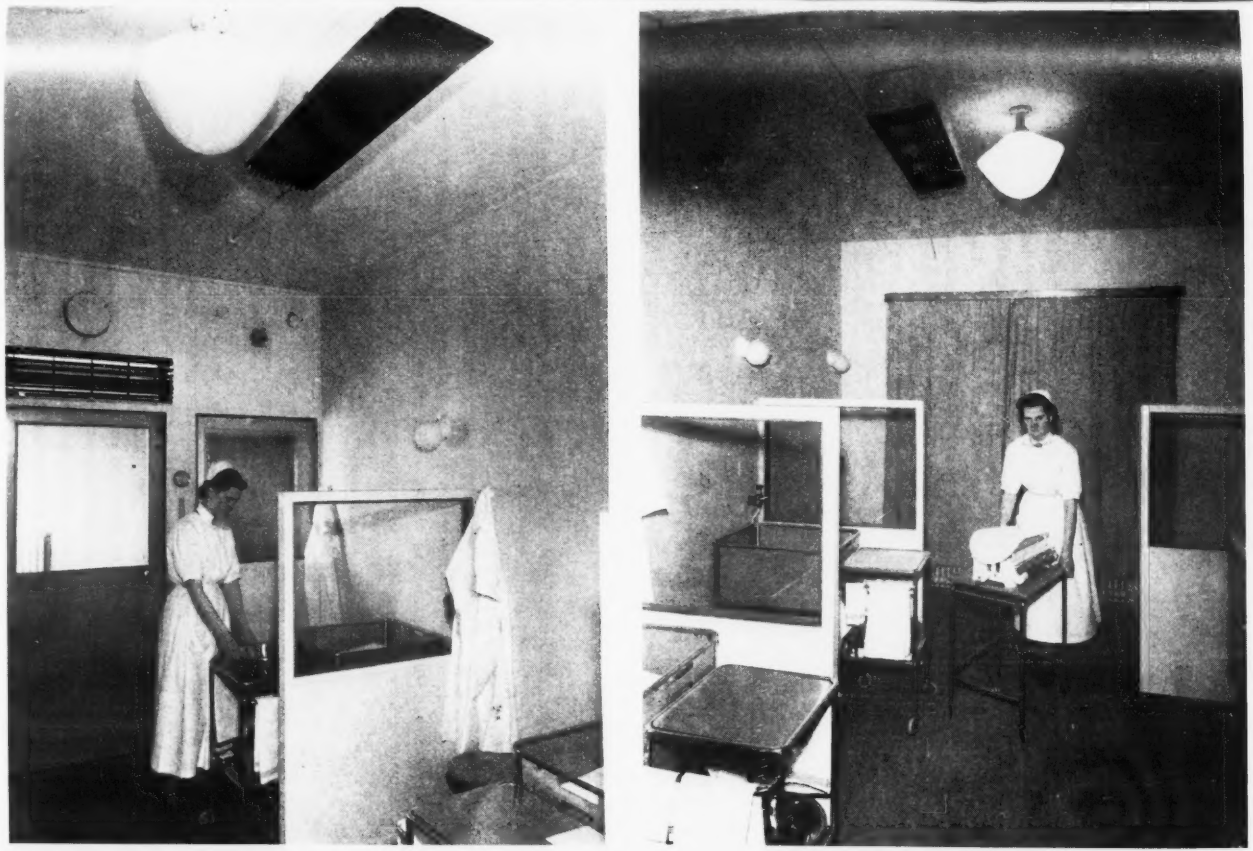

Fig. 2. One of the open ward units (Room 5). Above the door (left-hand picture) is seen the fitting for upper air irradiation. The fitting on the ceiling is for curtain irradiation.

2. They are successively transferred to Rooms 3, 4 and 5, which are open wards for 4 patients, with the beds separated by a wall reaching half-way to the ceiling (see Fig. 2). The room for breast-feeding contains 6 cubicles for sitting and 1 for lying down.

The department is entirely air-conditioned. The air is forced from the filter, humidifier, and heating units both through perforations in the ceiling into the corridors, and through vents directly into the patients' and breast-feeding rooms. The air pressure is kept somewhat higher in the corridors than in the rooms. The ventilation rate is 3–5 air changes per hour for Room 1 and the room for breast-feeding, and 5–7 air changes per hour for Rooms 2–5. These values for the ventilation rates were measured with the current technique, using a hydrogen-gas katharometer. The temperature in Rooms 1–3 is 22°C and in Rooms 4 and 5, 19°C. The humidity of the air can be varied from 40 to 70 per cent. It is controlled in the individual room by means of a hair hygrometer and, during the observation period, was usually kept at 60 per cent.

Physical Principles

The adequate physical measure of the quantity of bactericidally effective radiation obtained from ultraviolet equipment in a room is expressed as the product of the bactericidal flux emitted by the fittings and the average length of the rays. The dimension is thus watt-meter. By dividing this measurable and computable value by the volume of the room, the *mean room intensity* is obtained; its dimension is thus watt/m^2 (1 W/m^2 = 100 μW/cm^2). This calculation, which has been used in earlier investigations (Ronge 1948), is made from the following equation:

$$E = \frac{\Sigma (\Delta F \cdot R)}{V}$$

where E is the mean room intensity in watt/m^2, ΔF is the energy output in watts of the fitting at different angles, R is the ray length in meters for each such angle and V is the volume of the room in m^3.

In order to make optimal use of the available bactericidal radiation (F), the lamps must be placed so that the longest possible ray length (R) is obtained. The fittings for horizontal radiation should therefore be placed on the short sides of the room.

In occupied rooms, the total ultraviolet output is limited by the following factor: the irradiation intensity in the lower part of the room must not exceed the value that may give rise to actinic eye irritations (keratitis, conjunctivitis). According to the American standard (Council on Physical Therapy), this safety intensity is 0.5 μW/cm^2, with 8 hours' exposure per 24 hours, and 0.1 μW/cm^2 with 24-hour exposure.

The mean room intensity may, however, be considerably higher than this safety intensity. This is achieved by strong irradiation of the volume of the room above normal eye level, i.e., *upper air irradiation*. In order to maintain a sufficiently high intensity at this level, without exceeding the safety intensity in the lower part of the room, the lamps must be placed in reflectors well screened downwards. In addition, the ceiling and the upper part of the walls must be painted with an ultraviolet-absorbing paint, such as matt oil-paint. Since ordinary lime-wash reflects up to 50 per cent of the ultraviolet radiation, it cannot be used.

The bacterial count of the air must be kept low in the parts of the room that are not directly irradiated. For this purpose, the *vertical circulation of air* between the irradiated and unirradiated zones must be sufficiently high to permit a continuous

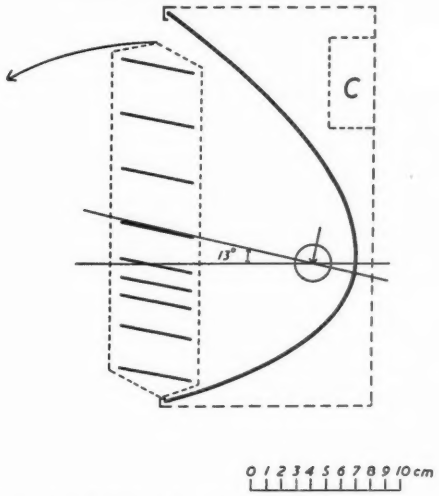

Fig. 3. Sectional diagram of wall fitting. In front of the aluminium sheeting, bent in a parabola, is seen the set of parallel screens, mounted in a movable frame. C = the coil.

dilution with irradiated air from above. The resulting practical efficiency of the equipment depends to a very high degree on this factor.

Under certain conditions, *vertical curtains* of irradiation from reflectors sharply screened from the sides can also be used to increase the mean room intensity. In such curtains, the safety intensity is exceeded by about 1,000 times. They can, however, be used in departments for infants for irradiation between the cubicles. They can also be used in entrances to cubicles and in corridors through which the staff pass rapidly. With such a vertical curtain, there is a risk of eye damage only on looking directly up at the fitting.

Lamps

The lamps were 30- and 15-watt, low-pressure, mercury discharge tubes of the type generally used for ultraviolet air disinfection. The smaller lamps (15 watt) were used in the cubicles for prematures, one in each cubicle. (The lamps were kindly supplied by Lumalampan AB, Stockholm.) When new, the unscreened 30-watt lamp has an output of 7 W at 2,537 Å, corresponding to a radiation intensity of about 60 μW/cm² at a distance of one meter from the tube. Both before and during the experiments, the radiation intensity of the lamps was measured, using the methods described below.

Fittings

The fittings were of two kinds: a *wall fitting* for upper air irradiation, and a *ceiling fitting* for curtain irradiation. The reflectors used in both types of fitting were of shiny aluminium sheeting, with no special surface treatment. The metal was bent into a parabolic shape, as shown in the sectional diagram (Fig. 3). A set of parallel

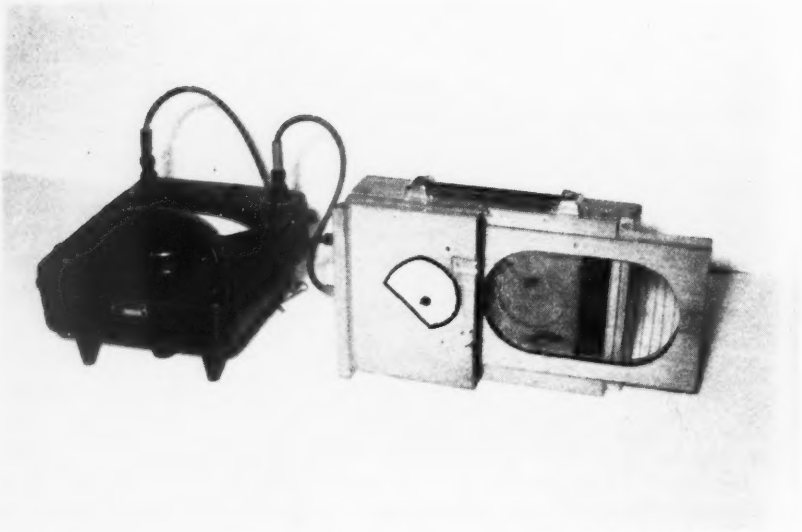

Fig. 4. The instrument used for the radiation measurements. In this type, a Diofan filter is used for selective absorption of the bactericidal radiation (cf. text).

screens was mounted in the opening of the fitting, in order to steer the radiation in the desired direction. Considerable difficulty was encountered in finding a surface treatment for the screens that did not cause disturbing reflections. The problem was finally solved by using so-called optical black, which gave a surface practically free from reflectivity. The screens in the curtain fittings were made somewhat higher than in the wall fittings, and were closely spaced in order to make the beam more concentrated.

The intensity distribution from the fittings was determined by measurements in an optical bench. For the wall fitting, the highest intensity was measured in an obliquely upward direction from the reflector (12° elevation above the horizontal plane), and amounted to 325 $\mu W/cm^2$ at a distance of 1 meter. The degree of efficiency in the central plane was calculated from the intensity distribution curve to be about 30 per cent. The appearance of the fittings is shown in the photographs (Fig. 2).

Radiation Intensity Measurements

The following instrument was constructed for measurement of the bactericidal component of the ultraviolet irradiation from the lamps by means of a selenium barrier-layer photocell (see Fig. 4). The principle of the method is a *filter difference measurement*, since the bactericidal component cannot be directly measured. The surface of the photocell is covered by the ultraviolet-transparent but light-absorbing UG5 filter. It is first exposed in this state directly to the ultraviolet radiation, and the intensity is read off on the galvanometer. This is followed by a second determination in which the radiation is allowed to pass through an additional filter in front of the photocell. This filter selectively eliminates the bactericidal component of the

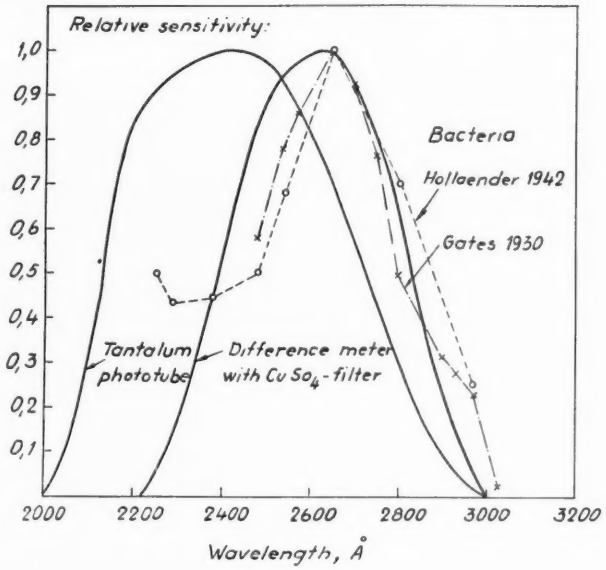

Fig. 5. The relative spectral sensitivity of the instrument in which a copper sulphate filter is used for the difference measurements. The diagram also shows the spectral sensitivity curve of the bacteria in question according to GATES and HOLLAENDER, and the spectral sensitivity of a tantalum phototube.

radiation. The intensity of the latter is then obtained as the difference between the two measurements. If the instrument is to be utilizable for measurement of the bactericidal radiation from different kinds of light sources, its spectral sensitivity curve must coincide with the bactericidal action spectrum. This necessitates a filter of which the relative absorption spectrum is in agreement with the bactericidal action spectrum.

Before a selenium photocell can be used for measurement of ultraviolet radiation with wave-lengths below 2,800–2,600 Å, its surface layer of lacquer must be removed. This is most simply done with acetone. The photocell will then have a very constant and even ultraviolet sensitivity, which slowly decreases towards the short-wave range. At 2,500 Å, the sensitivity is about 65 per cent of that at 4,000 Å, the corresponding figure at 3,000 Å being about 80 per cent. The built-in UG5 filter also serves to protect the surface of the photocell.

The filter found to be most suitable for selective elimination of the bactericidal ultraviolet radiation is a *0.20 per cent aqueous solution of copper sulphate*, contained in a quartz cuvette as a layer 2 cm thick. In combination with a 3-mm UG5 filter, the spectral sensitivity curve shown in Fig. 5 is obtained in a difference measurement. This figure also shows the bactericidal action spectrum according to different authors, as well as the spectral sensitivity of the tantalum phototube often used in the U.S.A. for ultraviolet radiation measurements. The method described was used for the *laboratory measurements* of the radiation intensity of the lamps before and during the experiments.

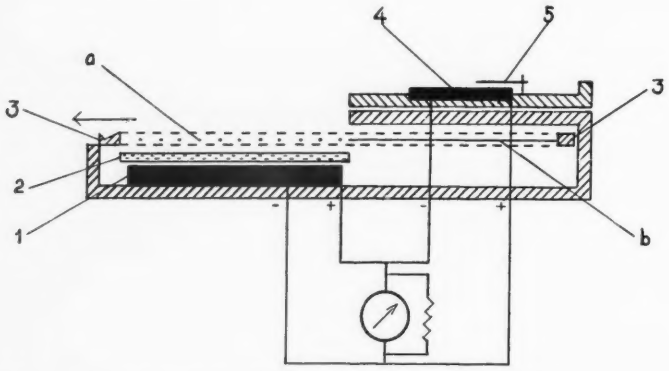

Fig. 6. Schematic drawing of the Diofan-filter instrument for difference measurements. 1 = selenium photocell. 2 = UG5 filter. 3 = movable frame with thin silver threads (*a*) and 0.05 mm Diofan foil (*b*) in the respective halves. 4 = small selenium photocell for balancing the galvanometer reading. 5 = movable diaphragm in front of the small photocell.

For the *field investigations*, it was found suitable to replace the copper sulphate quartz filter by a *0.05 mm thick foil of cellulose acetate* ("*Diofan*"). This provided a small and easily transportable instrument (see Fig. 4). A schematic diagram of the construction and wiring of this Diofan difference instrument is seen in Fig. 6. During the measurement, the movable frame is first shifted to the open position. (The only purpose of the thin, black silver threads is to compensate for the losses of reflection in the subsequent measurement with the Diofan filter.) If the reading is beyond the galvanometer scale, it can be brought back by opening, to a suitable degree, the diaphragm in front of the small balanced photocell in the lid of the instrument. When the reading has been made, the frame is shifted, so that the Diofan filter covers the surface of the photocell. After a new reading and subtraction, the relevant intensity of the bactericidal radiation is obtained.

Both variations of the instrument were calibrated by simultaneous measurements on low-pressure mercury lamps with a tantalum photocell. The spectral sensitivity of the phototube is known, and its absolute sensitivity was controlled by thermopile measurements. The sensitivity of the difference instrument was found to be 0.15 μW/cm^2 per mm of the galvanometer reading for radiation with a wave-length of 2,537 Å. This sensitivity is satisfactory for most purposes. By using a high-sensitivity light-spot galvanometer, the sensitivity could be increased about 10 times.

Bacterial Air Spray

The bactericidal effect of the ultraviolet equipment was determined by means of counts of bacteria sprayed into the air. The spray used is constructed by Roots & Petersen and has been described in earlier papers (Rooth, Laurell *et al.*). It gives an aerosol with a very even particle size of 1–3 μ. The time required to obtain a suitable concentration of bacteria for each experimental series varied appreciably, and had to be tried out for each individual species. As a rule, the initial concentration was about 3,000 bacteria per 100 liters of air.

Bacterial Air Sampler

Airborne bacteria, both sprayed and naturally occurring, were collected with a BOURDILLON slit-sampler having an air flow of 33 liters per minute. Since sprayed bacteria are rapidly destroyed by exposure to ultraviolet irradiation, a short exposure time (30 sec.) was used, and a new plate was exposed once a minute.

In the determination of the naturally occurring bacteria, the plates were exposed for 3 minutes, with a new plate every 5 minutes.

Cultural Technique

The following bacteria were used in the spray tests: *B. prodigiosus*, *E. coli*, and *Staph. albus*; the two last-mentioned were isolated from the air in the wards. They were cultured on ordinary nutrient broth, and 16 to 18-hour cultures were used for spraying. In the collection of samples, both of sprayed and of naturally occurring bacteria, with the Bourdillon apparatus, nutrient agar plates containing 10 per cent horse blood were used. After exposure, the plates were incubated at 37°C for 20 to 24 hours. A count was then made of the number of colonies.

Results

General Experience

Before starting to use the ultraviolet equipment, instructions were given to the staff regarding the safety measures to be observed in order to avoid radiation injuries. As far as the lamps in fittings for upper-air irradiation were concerned, the risk of direct irradiation was extremely slight. In practice, the curtain fittings were also found to cause no inconvenience. During the two years the equipment has been used, only two cases of radiation injury (conjunctivitis) have occurred. Both were caused by neglect of the safety measures prescribed. There were no cases of radiation injury among the children nursed in the wards.

During the first months, some of the staff complained of headache. It was found that this could probably be ascribed to the fact that—owing to a misunderstanding—the ordinary lighting had not been turned on in the afternoon, but the work had been done in the faint blue light from the ultraviolet lamps. The slight production of ozone from the lamps caused no marked inconvenience.

Radiation Intensity and Distribution

In order to illustrate the distribution of the bactericidal radiation in one of the rooms, an extra finely pulverised fluorescent powder (zinc silicate), which is strongly fluorescent to ultraviolet light of the wave-length in question, was sprayed, and its fluorescence was photographed (Fig. 7). It is evident from the pictures that a sharply defined zone of irradiation was obtained from both types of fitting. This was confirmed by the radia-

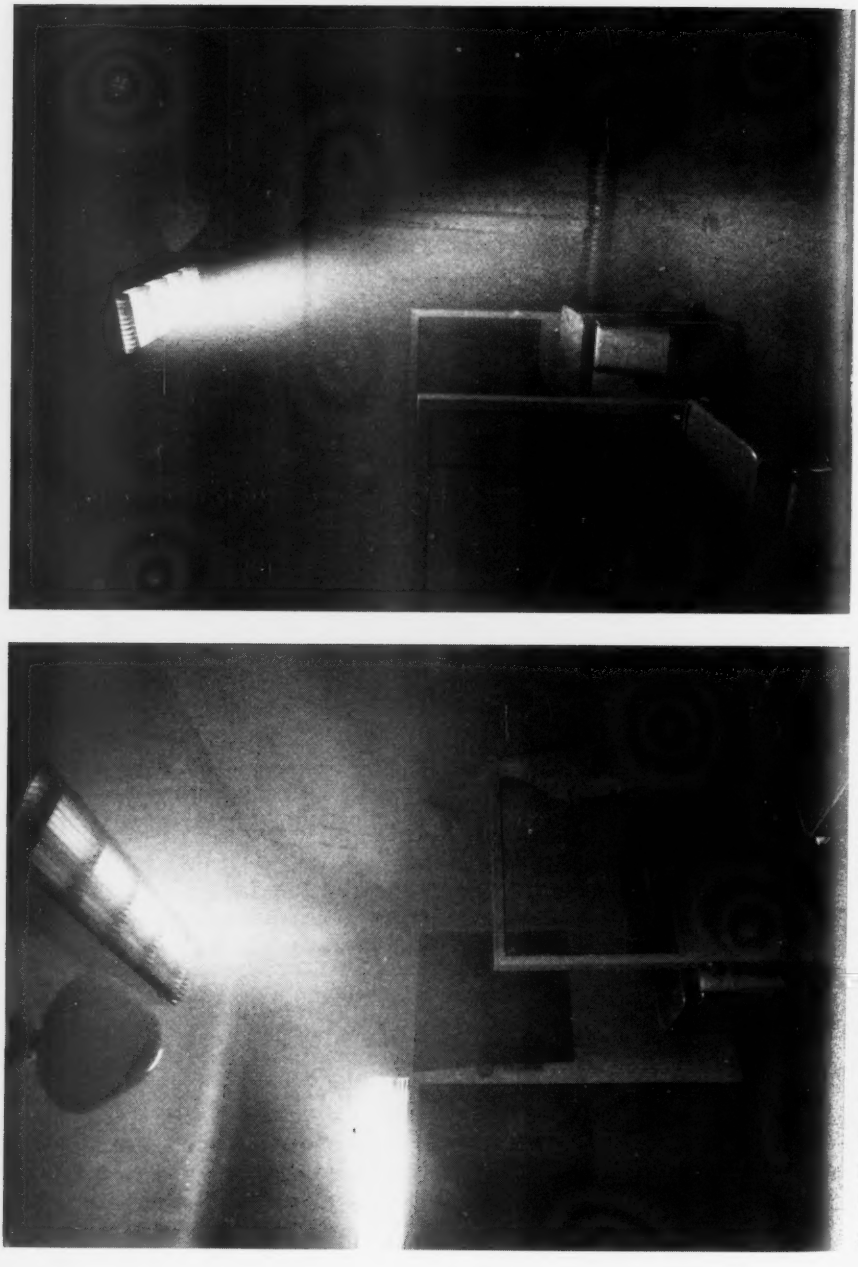

Fig. 7. Distribution of the ultraviolet irradiation in Room 5, illustrated by photographing the fluorescence from sprayed zinc silicate powder.

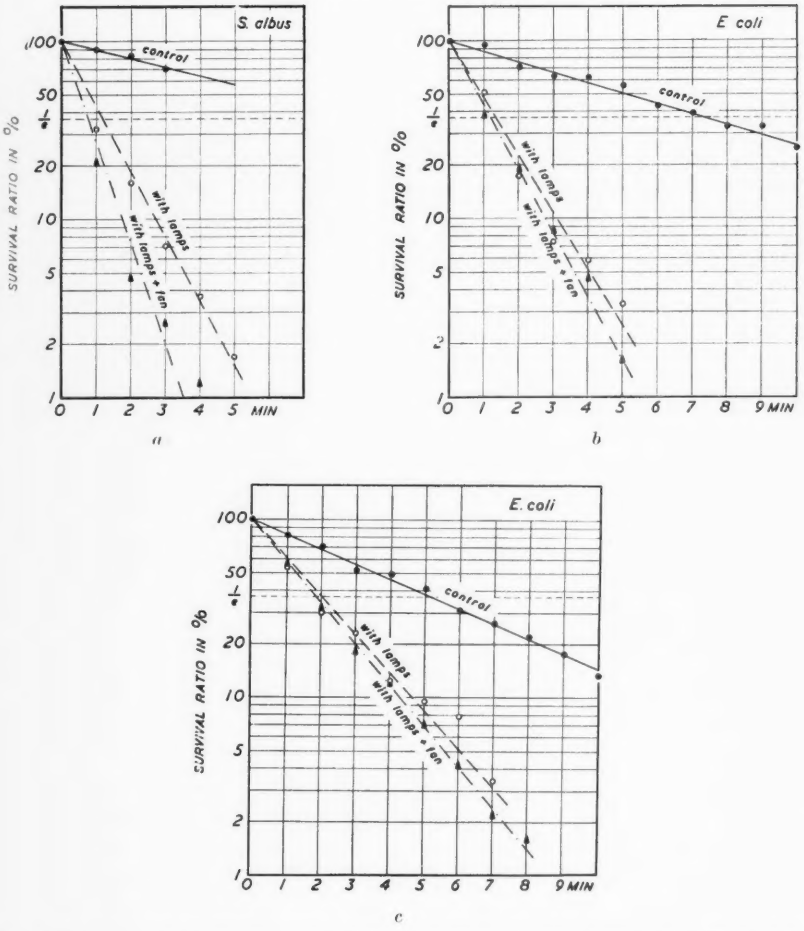

Fig. 8. Examples of the die-away rate of different kinds of sprayed bacteria in Room 5 (*a* and *b*) and in a cubicle for prematures (*c*). Plotted on semi-logarithmic paper. For explanation, see text.

tion intensity measurements. They showed, for example, that the intensity at the head of the most exposed cot was 0.5 $\mu W/cm^2$, that at the washing and changing table 0.1 $\mu W/cm^2$, and that at the least exposed cot 0.05 $\mu W/cm^2$, all calculated for the 2,537 Å wave-length. The mean room intensity was calculated to be 20–25 $\mu W/cm^2$ for Rooms 2–5.

Measurements of the radiation intensity of the lamps before and during the investigation showed their efficiency to have decreased to 58 from 82

Fig. 7. Distribution of the ultraviolet irradiation in Room 5, illustrated by photographing the fluorescence from sprayed zinc silicate powder.

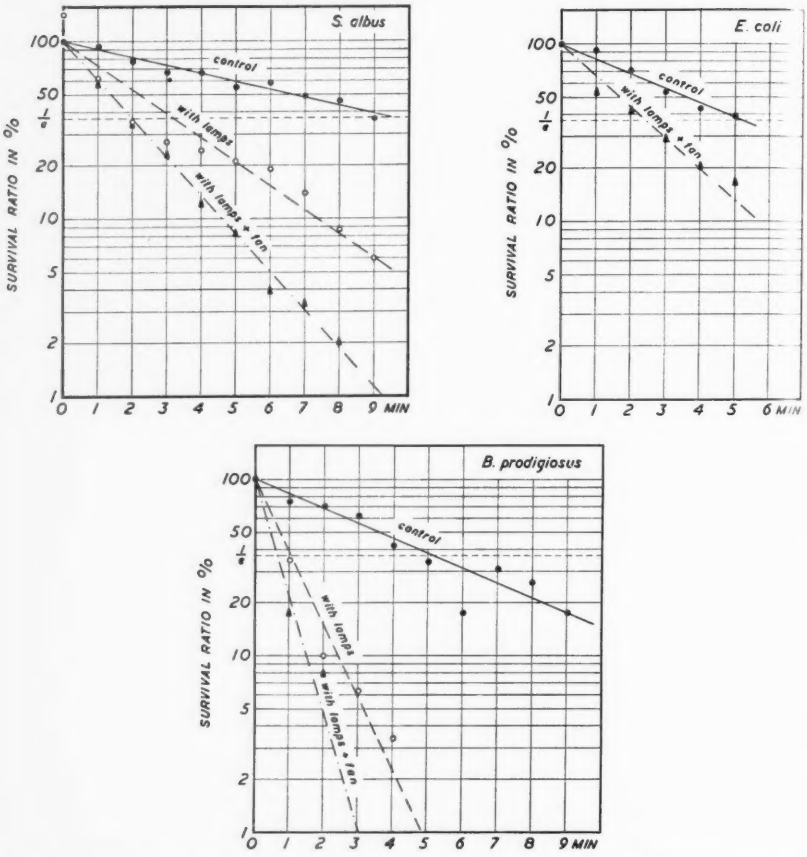

Fig. 9. Examples of the die-away rate of different kinds of sprayed bacteria in the room for breast-feeding.

per cent after one year's continuous use. The intensity of one lamp had fallen to 35 per cent.

Bacterial Counts: Sprayed Bacteria

The results of some typical determinations are assembled in graphic form in Figs. 8 and 9. It is seen that in all the experiments, the curve for the die-away rate in the air followed, as expected, an exponential course according to the equation

$$\frac{P}{P_0} = e^{-Nt}$$

TABLE 1

The die-away rates, expressed as equivalent air changes per hour, for sprayed bacteria.

n = number of tests.
M = mean value, with range of observations in brackets.

	Die-away rates					
	without irradiation		with irradiation		with irradiation + fan	
	n	M	n	M	n	M
1. Rooms 3–5						
E. coli	1	8	1	46	1	50
Staph. albus	1	7	2	58 (55–60)	2	93 (86–100)
B. prodigiosus	—	—	9	169 (100–300)	—	—
2. Room 1 (Premature cubicle)						
E. coli	1	12	1	30	1	31
Staph. albus	—	—	1	29	1	40
B. prodigiosus	2	18 (17–18)	4	94 (75–120)	—	—
3. Breast-feeding room						
E. coli	2	9 (8–11)	—	—	2	18 (14–21)
Staph. albus	2	7 (6–7)	2	21 (20–21)	2	28 (26–29)
B. prodigiosus	2	11 (10–12)	4	57 (46–67)	3	73 (46–86)

where P is the bacterial concentration at time t, P_0 is the bacterial concentration when sampling is started ($t = 0$), e is the base in the natural logarithmic system, and N is the die-away rate expressed as the number of equivalent air changes with sterile ventilating air in the room. When the ratio P/P_0 has fallen to a value of $1/e$, corresponding to a survival ratio of 36.8 per cent, the equation provides the following simple solution for N:

$$N = \frac{1}{t}.$$

In the diagrams, the survival ratio $1/e$ is denoted by a broken line. The point of intersection of this line and the killing curve gives the time for a reduction in the bacterial count of the air corresponding to one equivalent

TABLE 2

Relative increase in die-away rate produced by ultraviolet irradiation for different bacteria in Rooms 2–5. The increase is expressed as the ratio of the die-away rates with and without lamps.

Bacteria tested	No. of ratios	Range of relative increase in equivalent ventilation rate
		Times
Sprayed bacteria		
E. coli	2	6– 7*
Staph. albus	4	8–14*
B. prodigiosus	9	15–30
Naturally occurring bacteria		
Total count	27	1.4 (±SD 0.5)
α-streptococci	16	2.3 (±SD 1.3)

* The higher values were found when the air circulation in the room was increased by fans.

air change. The equivalent ventilation rate per hour is then computed from this value. The values thus obtained in all the experimental series are assembled in Table 1.

The results of the experiment recorded in Fig. 8 a (*Staph. albus*: Room 5) show that, without irradiation, the staphylococci disappeared from the air at a rate corresponding to about 7 air changes per hour. The killing rate during ultraviolet irradiation, on the other hand, corresponds to a ventilation rate of 58 air changes per hour. When the air circulation in the room was increased by means of a fan, the equivalent ventilation rate rose to 93 air changes per hour. Thus, the lamps brought about an approximately eightfold increase in the die-away rate, the increase with both lamps and fan being about 14 times (see Table 2).

In another experiment in the same room, using *E. coli* as the test bacteria, the corresponding values for the equivalent ventilation rate were 8, 46, and 50 air changes per hour, respectively. The relative increase in the die-away rate was thus 6–7 times.

In one of the cubicles for prematures (Fig. 8 c), the following values were obtained with *E. coli*: without irradiation 12, with irradiation 30, and with both irradiation and fan 31 equivalent air changes per hour. Consequently, in this case, the lamps brought about an increase in the die-away rate corresponding to an increase in the ventilation rate of scarcely three times.

In the room for breast-feeding (Fig. 9), the equivalent ventilation rate for *Staph. albus* was 7 changes per hour without irradiation, 21 with

radiation and 28 with both irradiation and fan. The corresponding values for *B. prodigiosus* were 11, 57 and 73 air changes per hour, respectively.

Bacterial Counts: Naturally Occurring Bacteria

Determinations of the effect of irradiation on the total number of naturally occurring airborne bacteria were all made in Room 2. The results of the individual measurements varied somewhat, for several reasons. Owing to the relatively low concentration of bacteria, it was necessary to extend the experimental periods over several hours. The possibilities of maintaining constant experimental conditions for such a long time were limited. For example, the experimental periods often coincided with such activities as bed-making or cleaning, when the air content of bacteria and dust can be expected to be particularly high and rapidly changing.

Consequently, when analyzing the results, the ratio of the bacterial count without and with the lamps turned on was first calculated for each experiment separately. The mean value of all the ratios was then computed (see Table 2). The mean value of the ratios for the total count amounted to 1.4, the standard deviation being 0.5 and the standard error of the mean 0.1. This implies that the lamps had a disinfective effect corresponding to an increase in the ventilation rate of 1.4 (i.e., 40 per cent).

Counts were also made of *Str. viridans* on the exposed plates. These bacteria could be assumed to have been conveyed to the air mainly from the patients and the staff. If the calculations are made in view of these bacteria only, the ratio is higher, namely 2.3 (standard deviation 1.3 and standard error of the mean 0.3).

Discussion

An account has been given of the experience gained in the installation and use for two years of ultraviolet irradiation equipment for air disinfection in a children's hospital. The equipment has hitherto been found effective from both the bacteriologic and technical viewpoints, and is associated with no risks of radiation injuries to patients or staff. It has been found surprisingly easy to adapt the ultraviolet irradiation to the daily hospital routine, and it has caused little inconvenience.

The effectivity was studied both with physical methods, by means of measurements of the radiation intensity, and by bacterial counts of the air.

Measurements showed that the fittings and their installation were satisfactory, and that the mean room intensity could be kept at 20 to 25 $\mu W/cm^2$. In order to ensure a full effect, it is advisable to change lamps of the type in question after about 18 months' continuous use. The radiation

intensity in the lower occupied part of the rooms was found to be higher at several points than that recommended in American standards. In conformity with the experience in England, this produced no ill-effects. This can presumably be explained partly by the kinetics of the photo-actinic effect on long exposure (RONGE 1951).

A question of great importance was to demonstrate that the equipment was really effective from the bacteriological viewpoint. This was tested by determinations of the die-away rate of bacteria sprayed into the air. The effect could then be determined on this basis, by the usual method of calculating the number of equivalent air changes per hour.

The results of these computations showed a good bactericidal effect on the bacteria used for the tests. For example, in the cubicles for prematures, the number of equivalent air changes during irradiation was 30 per hour, and in the larger rooms 40 to 50 per hour. When the air circulation was increased by means of a fan, an improvement was noted; the equivalent ventilation rate was then as high as 85 to 90 air changes per hour in some cases. It may be mentioned as a comparison that, without irradiation, the normal die-away rate of the sprayed bacteria ranged from 9 to 12 changes per hour.

The experiments in the room for breast-feeding were of particular interest. Here, the results were consistently poorer, and the equivalent ventilation rate for both *E. coli* and *Staph. albus* amounted to only 19–21 changes per hour. This lesser effectivity in the room for breast-feeding must presumably be attributed to the fact that it is larger than the wards, and that the screened-off cubicles hamper the air circulation. Values of about 55 changes per hour were, however, obtained with a highly ultraviolet-sensitive organism such as *B. prodigiosus*. This good result is interesting in view of the fact that the investigations cited in advertising matter are often performed with *B. prodigiosus*. From the clinical standpoint, this bacteria is of less interest. Consequently, it is preferable to test the effectivity of ultraviolet equipment with bacteria having the same radiation sensitivity as pathogenic microorganisms.

In investigations of the bacteria normally occurring in the air, the results were considerably poorer than with sprayed bacteria. This observation has been made by several workers (BOURDILLON *et al.*, WILLIAMS). In all probability, a number of factors are responsible for the poor results. Several of the microorganisms normally present in the air, such as *B. subtilis* and various species of *Sarcina* have a comparatively low sensitivity to ultraviolet light. Other bacteria are conveyed to the air to a great extent in a dried condition and are bound to dust particles. In this state, even the pathogenic bacteria are more resistant to irradiation. A diffe-

entiation between non-pathogenic and pathogenic bacteria nevertheless showed that there was a greater reduction in the former as compared to the total number of bacteria.

Summary

An installation of ultraviolet lamps for air disinfection in the department for premature infants (20 beds) of a children's hospital has been studied during two years from both physical-technical and bacteriological points of view. The irradiation was performed by upper air and curtain irradiation with the lamps turned on throughout the 24 hours. The mean room intensity in the wards was 20–25 μW/cm² of radiation of the wave-length 2,537 Å, the intensity at the cots amounting to about 0.5 μW/cm². No radiation injuries were noted. A simple and inexpensive instrument for intensity measurements of bactericidal radiation was constructed. Tests with sprayed bacteria showed an air disinfection by the lamps equivalent to 29–169 air changes per hour, corresponding to a relative increase, 6–30 times, in the disappearance rate of airborne bacteria without irradiation. *B. prodigiosus* was found to be considerably more sensitive to the irradiation than species of ordinary pathogenic microorganisms. Studies on naturally occurring bacteria showed that the irradiation achieved only a 40 per cent increase in the disappearance rate with respect to the total counts and a relative increase of 2.3 with respect to the counts of naturally occurring *Str. viridans*.

Désinfection de l'air par les ultra-violets dans un hôpital d'enfants. Etude technique et bactériologique.

Une installation de lampes à ultraviolets pour désinfection de l'air, dans le service de prématurés de 20 lits d'un hôpital d'enfants, a été étudiée pendant 2 ans, au double point de vue technique et bactériologique. L'installation était réalisée par une irradiation, de l'air des parties hautes, à l'aide de lampes fonctionnant pendant les 24 heures. L'intensité moyenne obtenue dans les salles était une irradiation de 20–25 W/cm² pour une longueur d'ondes de 2537 Å, et atteignant 0,5 μ W/cm² au niveau des lits. Aucun accident d'irradiation n'a été enregistré. Un instrument simple et peu couteux pour la mesure de l'intensité de l'irradiation bactéricide a été construit. Des études bactériologiques ont montré une désinfection aérienne par les lampes équivalente à 29–169 renouvellements de l'air par heure, et correspondant à une amélioration de 6 à 30 fois de la vitesse de disparition des bactéries aménées par l'air, par rapport à ce qu'elle était avant l'irradiation. Le Bacillus prodigiosus a été trouvé beaucoup plus sensible à l'irradiation que les autres races habituelles de microorganismes pathogènes. Les recherches sur les bactéries habituelles ont indiqué que l'irradiation assurait une augmentation de 40 % dans le taux de disparition du nombre total des bactéries, et un accroissement de 2.3 sur le taux du streptocoque viridans habituel.

Ultraviolett-Luftdesinfektion in einem Kinderkrankenhaus. Eine technische und bakteriologische Studie.

Der Einfluss von Ultraviolettlampen zur Luftentkeimung in einer Frühgeborenenabteilung (20 Betten) eines Kinderkrankenhauses wurde über 2 Jahre von physikalisch-technischen und bakteriologischen Gesichtspunkten aus geprüft. Die Bestrahlung

wurde von oben über 24 Stunden durchgeführt. Die mittlere Raumintensität in den Krankenräumen betrug 20–25 μW/cm² Bestrahlung einer Wellenlänge von 2537 Å, die Intensität an den Betten etwa 0,5 μW/cm². Strahlenschädigungen wurden nicht beobachtet. Ein einfaches und billiges Instrument zur Intensitätsmessung der bakteriologischen Bestrahlung wurde konstruiert. Bakterientests zeigten eine Luftentkeimung durch die Lampen, welche 29–169 Luftwechsel pro Stunde entsprachen, in Übereinstimmung mit einem relativen 6–30fachen Ansteigen der Abnahmerate von Luftkeimen ohne Bestrahlung. B. prodigiosus erwies sich als strahlenempfindlicher als Arten gewöhnlicher pathogener Mikroorganismen. Studien über natürlicherweise auftretende Bakterien zeigten, dass durch Bestrahlung nur ein Anstieg der Abnahmerate um 40 % erreicht wird — in Beziehung zur Gesamtzahl — und ein relativer Anstieg von 2,3 in Beziehung zur Menge der natürlicherweise auftretenden Viridans-Streptokokken.

Desinfección del aire mediante luz ultravioleta en un hospital de niños. Estudio técnico y bacteriológico.

Durante dos años se estudió, desde el punto de vista bacteriológico y fisicotécnico, el funcionamiento de lámparas de lyz ultravioleta para desinfectar el aire en el departamento de prematuros (20 camas). La experiencia se llevó a cabo durante las 24 horas del dia irradiandose la parte superior del recinto y en forma de cortina. La intensidad media en el departamento fue 20–25 μw/cm² de irradiación de 2537 Å de longitud de onda. La intensidad en las cunas fué alrededor de 0,5 μw/cm². No hubo accidentes por radiación. Se construyó un sencillo y barato instrumento para medir la intensidad de irradiación bacteriologica. Pruebas con pulverización de bacterias mostraron una desinfección del aire equivalente a 29–169 cambios de aire por hora, correspondientes a un relativo aumento, 6–30 veces la desaparición de las bacterias nacidas en el aire sin irradiación. El B. prodigiosus apareció mas sensible a la irradiacion que otras espacies de microbios patógenos. La investigación sobre las bacterias habituales mostró que la irradiación aseguraba un aumento del 40 % en las tasas de desaparición del numero total de estas y un aumento de 2.3 en la tasa del estreptococo viridans habitual.

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A Comparison of the Endogenous Creatinine and Inulin Clearances in Children

by DANAE IKKOS and LARS STRÖM

Available data support the view that inulin clearance (C_{IN}) is a valid measurement of the glomerular filtration rate (GFR) in children. However, the measurement of C_{IN} in children presents certain technical difficulties, as a constant infusion of inulin is required to obtain accurate measurements of GFR. The endogenous creatinine, which is present in plasma at stable concentrations, would be the ideal substance in this respect, if this substance were excreted in man only by filtration at the glomeruli.

The literature contains many reports on comparisons of inulin and endogenous creatinine clearances. In most of these studies, the analytical methods used for the estimation of creatinine measure not only true endogenous creatinine, but also "creatinine chromogens". Therefore the results obtained can not be accepted as representative for the clearance of the "true endogenous creatine" (C_{CR}).

The aim of the present paper is to report a comparison of the clearances of inulin and true endogenous creatinine in children.

Material and Methods

The material of the present study consists of 39 children, 17 males and 22 females, ranging in age from 6 to 15 years.

Cases 1–20 were patients treated for different disorders (Table 1) in which involvement of kidney function was improbable. Group I (Cases 1–6) was taken as the control group. Group II (Cases 7–12)[1] consists of 6 patients in whom acidosis was induced by ammonium chloride, given in a dosage of 0.25 g/kg/day for 2–5 days before the clearance studies. Metabolic acidosis was induced in the eight patients (Cases 13–20)[1] of Group III. After a fasting period of 2 days, a carbohydrate-poor, fat-rich diet was given to these patients. The clearance studies were performed on the 2–4 day after the end of the fasting period. Cases 21–35 were patients with kidney diseases. In six of these (Cases 21–27, Group IV) the clearance studies

[1] Cases 7–20 were used in a study of P^{32} excretion which will appear separately.

TABLE 1

Case Nr.	Sex	Age years	Diagnosis	CO_2 in plasma mEq/L	R. Legal in urine	C_{CR}*	C_{IN}*	C_{PAH}*	F.F.†
1	M	10	Normal			123	111	494	0.22
2	F	15	Hypertension			132	124	563	0.22
3	F	15	Primary pulmonary tuberculosis			115	114	467	0.24
4	M	14	Primary pulmonary tuberculosis			148	125	644	0.19
5	M	10	Exud. pleuritis			141	116	490	0.23
6	F	8	Primary pulmonary tuberculosis			141	130	731	0.18
7	F	12	Primary pulmonary tuberculosis	15		116	80	390	0.20
8	M	11	Epileptic syndrome	14		183	155	684	0.22
9	F	14	Post primary pulmonary tuberculosis	20		118	81	560	0.15
10	F	8	Primary pulmonary tuberculosis	13		137	116	514	0.22
11	M	14	Obesity	15		115	138	590	0.23
12	M	13	Obesity	13		105	83	375	0.22
13	F	14	Obesity	18	+ + +	118	128	**	
14	F	14	Obesity	23	+ + +	171	132	493	0.27
15	M	12	Obesity	18	+ +	128	115	493	0.23
16	F	11	Obesity	13	+ +	125	119	531	0.23
17	M	11	Obesity	21	+ + +	125	120	426	0.28
18	M	8	Obesity	23	+ +	124	93	317	0.29
19	F	7	Obesity	25	+ +	113	108	496	0.22
20	M	13	Obesity	22	+ +	114	102	392	0.26
21	F	10	Subacute glomerulonephritis			178	118	354	0.33
22	F	10	Acute glomerulonephritis			166	115	806	0.14
23	F	9	Acute glomerulonephritis			104	109	560	0.19
24	F	7	Hematuria			144	103	456	0.22
25	F	13	Acute glomerulonephritis			108	88	**	
26	F	14	Renal tuberculosis			87	88	326	0.27
27	F	10	Acute glomerulonephritis			134	84	578	0.15
28	M	6	Acute glomerulonephritis			66	54	401	0.13
29	M	10	Acute glomerulonephritis			48	10	160	0.06
30	M	7	Lower nephron nephrosis			88	73	378	0.19
31	M	13	Acute glomerulonephritis			64	46	503	0.09
32	M	10	Steatorrea			88	63	181	0.35
33	F	6	Chronic glomerulonephritis			7	10	17	0.58
34	M	9	Lupus erythematosus disseminatus			15	12	44	0.27
35	F	6	Nephropathia			9	9	21	0.42
36	F	11	Diabetes mellitus		+ + +	156	160	489	0.32
37	M	10	Diabetes mellitus		−	157	140	534	0.26
38	F	8	Diabetes mellitus		−	126	133	611	0.22
39	F	9	Vit. D resistent rickets			308	143	548	0.26

* All values expressed in ml/min./1.73 m^2.

† Denotes filtration fraction.

** C_{PAH} was performed but did not succeed.

vealed values within the normal limits, while in the remaining (Group V) the clearance values were decreased. Finally 3 cases of diabetes mellitus (36–38) and a case of vitamin D resistent rickets (Case 39) were studied.

The measurement of the clearances of true endogenous creatinine (C_{CR}), inulin (C_{IN}) and paraminohippuric acid (C_{PAH}) were performed according to SMITH *et al.* The children were fasted since the previous evening. After control blood samples were taken, the priming injections of inulin and PAH were given and an approximately constant infusion of these two substances by the open drip method was started, at an appropriate rate. A period of one hour was allowed for equilibration of inulin and PAH into the body, after which three urine specimens were collected at periods of approximately twenty minutes. Urine was collected by an indwelling catheter, the bladder being washed at the end of each collection period with saline and emptied by injection of air and suprapubic pressure. Three to five blood samples were taken during the second hour and the concentrations of creatinine, inulin and PAH at the middle of each urine collection period were found by interpolation. In the calculations of the clearances no correction for urine delay time was done.

Plasma and urine were analysed: for creatinine by the method of HARE, on a trichloracetic acid filtrate; for inulin by SCHREINER's method of resorsinol; and for PAH, by the method of SMITH *et al.*

The statistical methods used were the conventional ones (EZEKIEL, BONNIER).

Results

The degree of acidosis induced in cases 7–20 is shown in Table 1. The carbon dioxide content of the plasma varied between 13–25 mEq/L and a two to three-plus positive test for acetone in urine was present in Cases 13–20.

The results of the measurements of C_{CR}, C_{IN} and C_{PAH}, expressed per 1.73 m² surface area are presented in Table 1. C_{IN} and C_{PAH} were within the normal limits in Cases 1–26 and 36–39 and decreased in Cases 28–35.

The changes in the plasma concentration of inulin during the test are presented in Fig. 1. Time 0 represents the beginning of the first urine collection period. The plasma concentrations of inulin at the middle of the second and third collection period were expressed in per cent of the 10th min. value and plotted against time. A decrease in the plasma concentration of inulin was found, amounting to 17.4 per cent between 0 and 60 min., this decrease being highly significant ($p < 0.001$).

Table 2 presents the $C_{CR}:C_{IN}$ ratio for each of three urine collection periods in each individual. A coefficient of variation of 13.54 per cent was found. The analysis of the variance showed no statistical difference between the $C_{CR}:C_{IN}$ ratios obtained at the three periods ($p < 0.1$) while the differences of $C_{CR}:C_{IN}$ between cases were highly significant ($p < 0.001$).

In Fig. 2 the $C_{CR}:C_{IN}$ ratio (mean for each case) is plotted against C_{IN} (ml/min./1.73 m² S.A.). No significant increase in the ratio of $C_{CR}:C_{IN}$

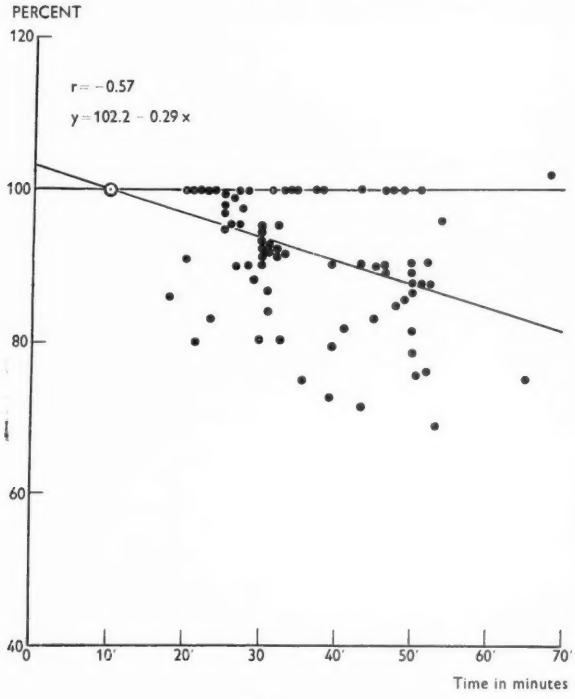

Fig. 1.

was found when the C_{IN} was decreasing, the coefficient of correlation being insignificant ($p > 0.1$).

The mean values for the $C_{CR} : C_{IN}$ ratio for the whole material and each one of the indivudal group are presented in Table 3. The largest variation (26.13 per cent) was found in Group V and the smallest in Group I. The mean values for the $C_{CR} : C_{IN}$ ratio in Group II, III and V did not differ significantly ($p < 0.1$) from the mean value in Group I, while the $C_{CR} : C_{IN}$ ratio was higher in Group IV compared to Group I ($p < 0.02$). The value in the three diabetic children (Case 36–38, Tables 1 and 2) lay within the limits the values in Group I, while the value in the case of vitamin D resistent rickets (Tables 1 and 2) lay well outside the limits of the values for Group I.

In Fig. 3, C_{CR} was plotted against C_{IN}. A highly significant correlation was found between the two clearances ($p < 0.001$). Regression equations were calculated for the whole material and for Cases 25–30 and 31–39 separately. They were found to be:

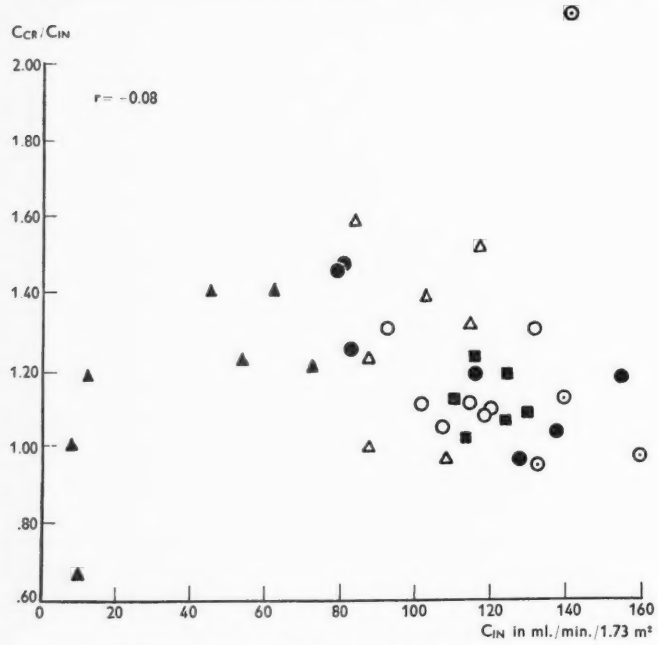

Fig. 2. (Symbols as legend in Fig. 3.)

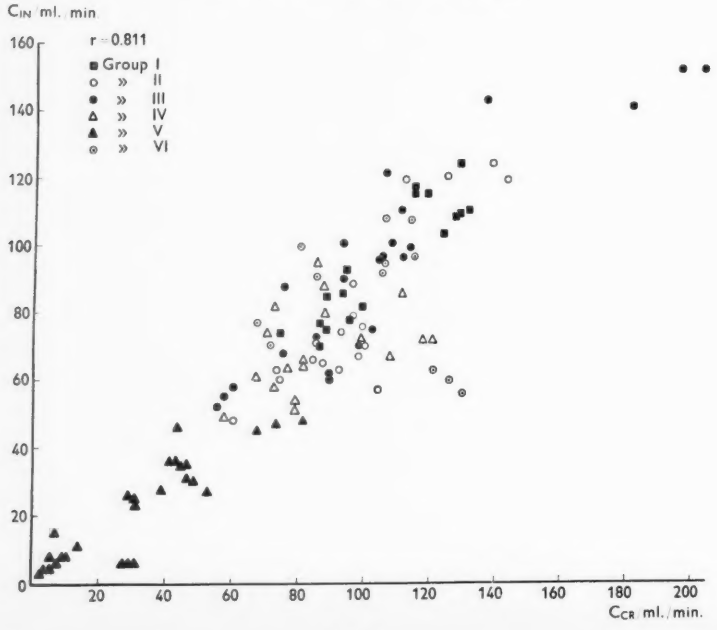

Fig. 3.

TABLE 2

$C_{Cr} : C_{IN}$ ratio.

Case Nr.	Period 1	Period 2	Period 3	Mean value	Case Nr.	Period 1	Period 2	Period 3	Mean value
1	1.17	1.19	1.00	1.11	21	1.29	1.60	1.67	1.51
2	1.03	0.98	1.19	1.06	22	1.42	1.66	1.23	1.32
3	1.02	0.99	1.01	1.01	23	0.93	0.87	1.10	0.96
4	1.18	1.20	1.17	1.18	24	1.45	1.16	1.56	1.39
5	1.20	1.22	1.22	1.22	25	1.25	1.25	1.18	1.23
6	1.03	1.09	1.12	1.08	26	0.99	1.10	0.89	0.99
7	0.43	1.47	1.48	1.46	27	1.57	0.92	1.49	1.58
8	1.09	1.20	1.25	1.17	28	1.33	1.26	1.11	1.23
9	1.83	1.35	1.27	1 47	29	4.95	4.76	5.13	4.98
10	1.18	1.15	1.23	1.19	30	1.22	1.25	1.14	1.20
11	1.11	0.94	1.03	1.03	31	1.60	1.93	0.93	1.40
12	1.22	1.31	1.24	1.26	32	1.47	1.34	1.40	1.40
13	0.95	0.86	0.92	0.96	33	1.11	0.77	0.48	0.67
14	1.29	1.33	1.28	1.30	34	1.26	1.15	1.13	1.18
15	1.15	1.14	1.05	1.11	35	0.93	0.96	0.87	0.92
16	1.03	1.08	1.08	1.08	36	0.98	1.13	0.80	0.97
17	1.14	1.04	1.09	1.09	37	1.12	1.05	1.19	1.12
18	1.44	1.40	1.11	1.31	38	0.94	0.89	1.01	0.95
19	1.05	1.04	1.05	1.05	39	2.11	2.34	1.91	2.11
20	1.18	1.35	0.86	1.11					

TABLE 3

Group	Mean	S.D.	S.E.	Coeff. of variation, %
I	1.11	0.09	0.02	8.2
II	1.21	0.23	0.05	18.60
III	1.15	0.14	0.03	12.50
IV	1.27	0.26	0.06	20.90
V	1.17	0.31	0.07	26.10
All cases	1.20	0.20	0.02	16.90

For the whole material,

$$C_{IN} = 19.00 + 0.64\ C_{CR} \pm 9.9 \text{ ml } (27.5\ \%)\ (1).$$

For Groups IV and V,

$$C_{IN} = 3.25 + 0.73\ C_{CR} \pm 11.08\ (25\ \%)\ (2)$$

and for Group V,

$$C_{IN} = 3.78 + 0.66\ C_{CR} + 5.73\ (26\ \%)\ (3).$$

The error of determination, expressed in per cent of the mean value, was approximately the same in all three equations.

Discussion

The fall in the plasma concentration of inulin during the second hour of the infusion is in accordance with the findings of GAUDINO *et al.* who showed that a time period of five hours of constant infusion is needed before inulin is completely equilibrated into its volume of distribution of the body fluids. However this change in plasma inulin level did not induce any systematic error in the comparison of the C_{CR} and C_{CI}, as no significant difference in the ratio $C_{CR} : C_{IN}$ obtained in the three periods was found.

Our findings are generally in agreement with previous reports which showed large variations in the $C_{CR} : C_{IN}$ ratios in kidney diseases (MATTER *et al.*). Although there was a tendency for the $C_{CR} : C_{IN}$ to increase when C_{IN} was decreasing, this tendency could not be verified statistically. Whether this finding depends on the few values for persons with deseased kidneys cannot be decided.

MILLER *et al.* have suggested that C_{CR} might be influen ed by factors not ordinary considered in clearance measurements. The present study failed to show any influence of acidosis produced by ammonium chloride or metabolic acidosis in this respect.

That the $C_{CR} : C_{IN}$ ratio was higher in children with clinical symptoms of kidney disease but normal clearances than in normal ! ildren is of special interest. The significance of this finding cannot be evaluated. Case 39 (D-vitamin resistent rickets) showed a $C_{CR} : C_{IN}$ ratio 2.11 although the C_{IN} and C_{PAH} were normal. This case was under treatment with ammonium chloride when the test was performed. However, the findings in Group II make such an explanation improbable. Nor can it be postulated that the disease *per se* induced these changes or in view of the findings of MILLER *et al.* in a similar case in an adult.

The $C_{CR} : C_{IN}$ ratio of 4.8 in Case 31 calls for special interest. The authors were unable to find a ratio higher that 2.5 in the literature. Unfortunately the test could not be repeated in this case.

Although a highly significant correlation is found between C_{CR} and C_{I}, the error of determination in the prediction of C_{IN} from C_{CR} is high, amounting to ± 27.5 per cent of the mean value. Accepting that C_{IN} represents a true measurement of GFR in children, as the available data strongly suggest, it is obvious that calculations of C_{IN} from C_{CR} are accompanied by such large errors as to make such calculations impractical.

HAUGEN and BLEGEN have recently reported a comparison of C_{CR} and C_{IN} in 18 subjects, 8 of whom had "hypertension, hyperthyroidism, nephrolithiasis and chronic nephritis of slight or moderate degree". These authors have found a $C_{CR}:C_{IN}$ ratio of 1.02, thus their results being different from those of others. The findings of HAUGEN and BLEGEN could not be confirmed in the present study. The method used by us for the determination of "true" creatinine was the same as theirs, the only difference being that trichloroacetic acid instead of sodium tungstade plasma filtrate was used. Whether this difference in the method can explain the difference in the results cannot be decided. It is however worth pointing out that the value of 1.02 found by HAUGEN and BLEGEN is not statistically different from that found by HARE *et al.*, the latter authors using trichloroacetic acid filtrate.

Summary

In 39 children the clearance of "true" endogenous creatinine, as measured by the aid of Lloyd's reagent, has been compared to the simultaneously measured clearance of inulin. The $C_{CR}:C_{IN}$ ratio was found to be 1.20 ± 0.22 and the accuracy of the prediction of C_{IN} from $C_{CR} \pm 19.9$ ml or ± 27.5 per cent of the mean value for C_{IN}. No significant differences in the $C_{CR}:C_{IN}$ ratio were found between normals or children made acidotic by ammonium chloride or ketogenic diet. A significant increase in the $C_{CR}:C_{IN}$ ratio was found in children with clinical findings of kidney disease but normal C_{IN} and C_{PAH} values.

Comparaison entre la clearance à la créatinine endogène et celle à l'inuline.

Chez 39 enfants, ont été comparés les résultats de mesures simultanées de clearance à l'inuline, et de clearance à la « véritable » créatinine endogène (mesurée à l'aide du réactif de Lloyd). Le rapport C_{CR}/C_{IN} a été de $1{,}20 \pm 0{,}22$, et la précision de la détermination de C_{IN} d'aprés C_{CR} de $\pm 19{,}9$ ml, c'est-à-dire $\pm 27{,}5$ % des valeurs moyennes de C_{IN}. On n'a trouvé aucune différence notable dans le rapport C_{CR}/C_{IN} en comparant des individus normaux, et des enfants rendus acidosiques par l'administration de Chlorure d'ammonium ou d'un régime cétogène. Une augmentation significative du rapport C_{CR}/C_{IN} a été mise en évidence chez des enfants présentant des signes cliniques de néphropathie, mais dont le chiffre de C_{IN} et de C_{PAH} étaient normaux.

Ein Vergleich der endogenen Creatinin- und Inulin-Clearence.

Bei 39 Kindern wurde die mit Hilfe des Lloyd-Reagens gemessene Clearance des „echten" endogenen Creatinins mit der gleichzeitig gemessenen Inulin-Clearance verglichen. Es ergab sich ein C_{CR}/C_{IN}-Verhältnis von $1{,}20 \pm 0{,}22$ und eine Genauigkeit der Vorausbestimmung von C_{IN} aus C_{CR} von $\pm 19{,}9$ ml oder $\pm 27{,}5$ % der Mittelwerte für C_{IN}. Zwischen normalen und mit Ammoniumchlorid oder ketogener Diät acidotisch gemachten Kindern wurden keine signifikanten Unterschiede in der C_{CR}/C_{IN}-Relation gefunden. Ein signifikanter Anstieg in der C_{CR}/C_{IN}-Relation wurde bei Kindern mit klinischen Zeichen einer Nierenerkrankung bei normalen C_{IN} und C_{PAH}-Werten festgestellt.

Comparación de la creatinina endógena con el clearance de inulina.

Por medio del reactivo de Lloyd, se midió, en 39 niños, el clearance de creatinina endógena "verdadera" comparándolo simultáneamente con el clearance de inulina. La relación C_{CR}/C_{IN} fué 1,20 $\pm$ 0,22. Si se determina C_{IN} del valor de C_{CR}, la precisión del cálculo será $\pm$ 19,9 o $\pm$ 27,5 % valor medio de C_{IN}. No se encontró diferencia significativa de la relación C_{CR}/C_{IN} comparando niños normales con niños en acidosis provocada por cloruru de amonio o dieta cetogénica. Un significativo aumento de la ralación C_{CR}/C_{IN} se encontró en pacientes con signos clínicos de enfermedad renal aunque las cifras de C_{IN} y C_{PAH} fueron normales.

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Idiopathic Hypoproteinaemia versus Hypoproteinaemia due to Pancreatic Dysfunction

by BO S. V. BILLE and BO VAHLQUIST

During recent years a number of reports has appeared on cases of hypoproteinaemia and oedema in children, which could not be explained by inadequate dietary protein, severe liver damage, or loss of protein in the urine. In some of these cases no satisfactory explanation could be found either during life or at necropsy, the condition being described as "idiopathic" hypoproteinaemia. In other cases signs of pancreatic dysfunction were noted. In the following we shall discuss briefly, in connexion with a case of pancreatic dysfunction with transitory, severe hypoproteinaemia, the relationship between idiopathic hypoproteinaemia and hypoproteinaemia associated with pancreatic dysfunction.

Case History

Parents healthy, of good social position, no blood-relations; mother gave no history of abortion.

First child, Lars Erik B., born 4.2.1948. Birth-weight 3.960 kg, breast-fed till 8 months. At 1 year developed frequent, bulky stools, and began to show poor weight-gain. At 16 months admitted to hospital for one month, and found to have moderate steatorrhoea with total fat in faeces 43.8 % (22 % of which was neutral fat). Duodenal intubation unsuccessful. Chest X-ray showed no pathological changes. The tentative diagnosis of coeliac disease was made. Slow improvement was maintained over the following years on a dietary regimen, but at 6 years of age the child still readily developed diarrhoea on infection or faulty diet. Weight- and height-gain, however, were normal, and there were no signs of bronchitis.

After cystic fibrosis of the pancreas had been diagnosed in his sister, the boy was reinvestigated. Pancreatic disease was discovered (see Table 1), but the paucity of clinical findings in the child, never treated with antibiotics or by substitution therapy, was striking.

Second child, Margaretha B., born 19.5.1954. Birth-weight 4.210 kg. Breast-fed child with poor weight-gain. At 4 months of age developed frequent, loose stools. Admitted to hospital 29.9.1954–21.1.1955. On admission pale and thin (weight at 4 months 5.2 kg). Oedema, especially of the face and extremities (Fig. 1). Rather potbelly but no definite signs of ascites. Slight exudative dermatitis.

Fig. 1 A. Margaretha B., aged 4 months, before treatment.

Fig. 1 B. Margaretha B., aged 7 months, after treatment.

TABLE 1

Laboratory Data.

	Case I (6 yrs.)	Case II	
		Before treatment (4 m.)	After (7 m.)
Blood			
Hb g %	12.6	7.1	10.9
Red cells $\times 10^6$	4.5	2.5	3.8
Haematocrit reading, %	35	25	35
Serum vitamin B_{12} mμg/ml	0.89	1.2	1.5
Electrophoretic analysis of serum			
Total protein (Kjeldahl's method)	6.8	3.6	5.8
Albumin %	40	32	49
Globulin α_1 %	6	7	8
,, α_2 %	13	20	13
,, β %	15	16	13
,, γ %	26	25	17
Albumin/globulin	0.7	0.5	1.0
Duodenal (fluid) after intravenous secretin			
Tryptic activity (Gross)	0	0	
Lipase activity units (Myers and Fine) (normal 0.3–4.3)	0.1–1.3	0.1	
Protein tolerance	path.	path.	path.
Fat tolerance	path.	path.	
Chest X-ray	peribronchial changes	0	opacities
Faeces			
Total fat %	44.2	62.2	
Neutral fat %	21.9	52.7	
Free fatty acids %	22.3	9.5	
Urine			
Albumin	0	0	0
Glucose	0	0	0
Amino acid pattern		normal	

Found to have hypoproteinaemia and anaemia. Duodenal fluid showed no trypsin activity, even after intravenous injection of secretin. Lipase activity pathologically low. (Table 1.) Protein tolerance test (gelatin) was performed 3 times. The rise in the amino acid nitrogen content of the plasma was slow and in two of the trials the maximum increase was less than 1 mg%.

Chest X-ray on September 30th was normal, but repeated examination on December 6th showed stringy opacities in the right middle and lower lobes. These subsequently

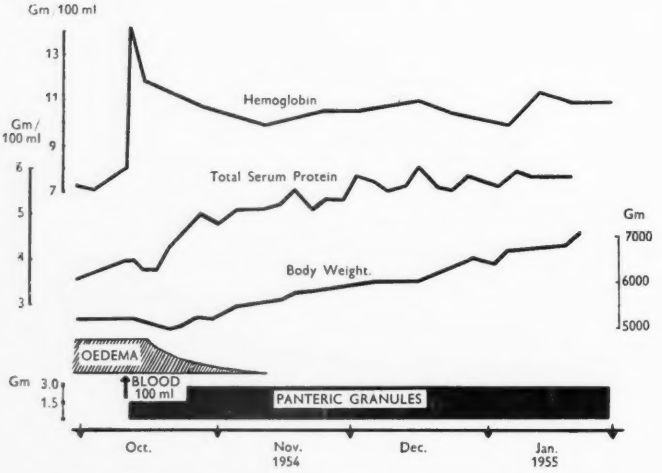

Fig. 2. Margaretha B., born May 19, 1954. Course of the disease.

diminished somewhat, but on January 10th there were still some opacities present in the lower lobe.

During the whole of her stay in hospital the child was given her mother's milk, with the addition, from October 29th, of citrated milk (200–300 g) and later of fruit juices, purees, and porridge. For two weeks initially she was given "Aminosolglucose" by mouth in a dose of 20 g per day (10 g casein hydrolysate). Treatment with 1.5 g per day of pancreatic enzyme (Panteric granules) was then begun on October 12th. Not until the dose was increased, two weeks later on, to 3 g per day, did the stools change for the better, the serum protein increase and the oedema disappear. (Fig. 2.) On discharge at 8 months of age the weight was 7.020 kg and the serum protein 5.8 g%, and the child was in very good condition. The diagnosis of pancreatic disease with hypoproteinaemia and anaemia (? cystic fibrosis of the pancreas) was made. At a follow-up examination at $11^1/_2$ months of age the child proved to be in an excellent condition with serum protein 6.5 g% and a normal electrophoretic pattern.

Discussion

The disease picture of the two siblings presented above should probably be classed as cystic fibrosis of the pancreas, but the paucity of clinical findings, especially in the boy, is striking. Cases of familial "hypoplasia of the exocrine tissue of the pancreas" with steatorrhoea and a tendency to oedema but without other gross signs of extra-pancreatic disturbances have been described (LUMB and BEAUTYMAN, 1952) and should be kept in mind.

In true cystic fibrosis of the pancreas the liver often shows changes of the "focal necrosis" type (see BODIAN, 1952). If these are very pronounced, interference with protein-synthesis would appear likely. In our case liver

function tests were quite normal and the rapid response of the hypoproteinaemia to treatment would make it seem probable that it had been due primarily to faulty utilization of the food proteins.

It is certainly remarkable that severe pancreatic dysfunction does not more regularly lead to hypoproteinaemia and oedema, especially so during the first year of life when the extremely rapid rate of growth places great demands on the supply and synthesis of protein. In our case the child was reared exclusively on her mother's milk (protein content in the 4th month of lactation 1.07 %, electrophoresis diagram normal). The same was the case in 6 of 8 children from the literature under one year of age in whom the mode of feeding is stated (Table 2). It is known that the casein of breast milk is broken down more slowly than that of cow's milk under the influence of gastric juice (MELLANDER, 1947), and thus more of it will pass into the intestine in peptide form. It would, however, appear that the homologous proteins are absorbed satisfactorily even when they are incompletely broken down, and the question of what part is played by the diet in the genesis of the hypoproteinaemia must for the present be left open.

A review of children with hypoproteinaemia and oedema lacking signs of proteinuria or grossly faulty nutrition is given in Table 2. The cases are classified according to the data concerning pancreatic function. Since pancreatic dysfunction of type other than mucoviscidosis is not necessarily associated with striking extrapancreatic changes, only direct statements concerning the function or morphology of the organ are acceptable in this connexion. It is seen that except for subgroups A and B only 3 children have been examined to the effect that the pancreas can be exonerated with reasonable certainty. To these cases another 3 may be added, in which recovery took place in a short time without specific treatment (HERTZOG *et al.*; ILLINGWORTH and FINCH; WYNGARDEN *et al.*). Still 6 other cases of "idiopathic" hypoproteinaemia remain in which the possibility of pancreas dysfunction cannot be ruled out.

In a number of the children pathologic changes were found in the liver at necropsy. In one child there was "atrophy" of the liver cells, in another interstitial fibrosis, either of which may have been concerned with the aetiology of the condition. In all other cases, however, the only finding has been fatty degeneration, the significance of which in the present connexion is more or less obscure.

Some other data are evident from Table 2. Twelve of the 23 patients were aged 0–6 months, only 5 being over 3 years; 14 out of 22 children were boys.

Oedema was present in all cases, and was the primary indication for closer examination of the state of the serum protein. As a rule it started

TABLE 2

Hypoproteinaemia and oedema in children, with or without pancreatic dysfunction.

Author	Sex	Age at onset	Serum proteins			Course and duration	Remarks
			Total %	Ratio	γ-glob. %		
A. Pancreatic dysfunction due to pancreatic fibrosis							
GLANZMANN 1946	♂	6 wks.	4.85	2.1		Died 6 wks.	P.M. findings: cystic fibrosis of pancreas; bronchiectasis; cirrhosis and fatty degeneration of the liver. (One brother died aged 9 wks.; oedema and hypoproteinaemia; serum-protein 4.0 % (albumin 4.0, globulin 0).)
FANCONI & BOTSZTEJN 1947	♀	6 wks.	4.66	6.1		Died 2 wks.	P.M.: cystic fibrosis of pancreas; bronchiectasis.
WISSLER & ZOLLINGER 1945	♀	7 wks.	4.6 3.2 4.5	1.9 0.8		Died 1 mth.	P.M.: cystic fibrosis of pancreas; bronchiectasis; haemosiderosis in liver, portal stasis.
FANCONI & BOTSZTEJN 1947	♂	2 mths.	4.6	1.5		Died 2 wks.	P.M.: cystic fibrosis of pancreas; bronchiectasis.
ØDEGAARD 1948	♂	3 mths.	3.5	0.6		Died 2 wks.	P.M.: slight cystic fibrosis of pancreas; widespread fatty degeneration of the liver.
JONES 1949	♂	3 mths.	3.0 4.1	 1.4		Died 7 wks.	P.M.: cystic fibrosis of pancreas; bronchiectasis; extreme fatty infiltration of liver.
BILLE & VAHLQUIST 1955	♀	4 mths.	3.6	0.5	25–17	Improved 8 mths.	No trypsin in the duodenal juice.
MENTEN & MIDDLETON 1944		15 mths.	5.5	reversed		Died	P.M.: cystic fibrosis of pancreas; liver mottled with small cream-coloured areas.
GARSCHE 1936	♂	5 yrs.	3.76			Died	P.M.: pancreatic fibrosis without cyst-formation; diffuse fatty degeneration of liver.
B. Pancreatic dysfunction without fibrosis							
LUMB & BEAUTYMAN 1952	♀	4 wks.	5.0	1.2		Died 8 mths.	No trypsin in the stools or duodenal juice. P.M.: glandular tissue of pancreas almost completely replaced by fat, with only a small quantity of granular tissue in the centre; complete absence of acinar elements, which were replaced by normal adult adipose tissue; no increase in fibrous tissue; islets normal.

Table 2 (cont.)

Author	Sex	Age at onset	Serum proteins			Course and duration	Remarks
			Total %	Ratio	γ-glob. %		
Illingworth & Finch 1954	♂	6 yrs.	4.2	0.6	a slight increase	Died 1 yr.	No trypsin in duodenal juice. P.M.: fatty infiltration of the pancreas without cystic fibrosis.
C. Pancreatic dysfunction probably not present							
Jonsson & Lagercrantz 1950	♂	18 mths.	2.6–4.8	0.5	13.5	Died 3 mths.	Normal protein-tolerance test. P.M.: Interstitial fibrosis and diffuse fatty degeneration of the liver.
Illingworth & Finch 1954	♂	2 yrs.	3.5	1.3	a negligible amount	Unimproved, 4 yrs.	Duodenal juice showed tryptic activity to a dilution of 1/320.
Falk & Laron 1955	♂	11 yrs.	3.2	1.3	7.4–15.8	Unimproved, 2 yrs.	Trypsin in faeces. Liver-biopsy normal.
D. State of pancreatic function uncertain							
Hertzog *et al.* 1950	♂	2 wks.	1.92	3.1		Healthy 18 wks.	The authors consider the cause to be "temporary abnormality in protein synthesis and catabolism".
Bound & Hackett 1953	♂	1 mth.	3.4	0.5 1.2	0	Unimproved, 21 mths.	Amino-aciduria. (One sister with oedema from birth died aged 6 mths.; serum protein 3.0; P.M.: fatty degeneration of the liver.)
Schick & Greenbaum 1945	♀	3 mths.	4.1	4.1	0	Unimproved, 12 yrs.	
Ødegaard 1948	♀	3 mths.	2.5	3.2		Died 2 wks.	P.M.: fatty degeneration of the liver cells.
Illingworth & Finch 1954	♂	7 mths.	3.8	0.9		Healthy 5 wks.	Followed up for 5 yrs.
Thompson *et al.* 1936	♀	15 mths.	3.4	1.3		Died 15 mths.	P.M.: atrophy of liver cells.
Salomonsen 1945	♀	2 yrs.	2.54	0.9		Unimproved, 4 yrs.	
Illingworth & Finch 1954	♂	3 yrs.	3.0	2.8		Healthy 14 mths.	Followed up for 2 years.
Wyngarden *et al.* 1952	♂	3 yrs.	3.14 4.6	0.7	4.3	Healthy 10 wks.	

in the face, hands, and feet, later becoming generalized in some cases. It was usually moderate in degree. Ascites was stated to be present in 9 cases.

The total protein was less than 3 g% in 4 cases, 3–4 g% in 12 cases, and more than 4 g% in 7 cases. The albumin/globulin ratio for the whole series varies from 0.5–4.1 (6.1), median 1.3. This differs from the state of affairs in nephrosis, where the figure is commonly about 0.5 or rather less. It is striking, however, that our case, like several of those included in Table 2, gave a comparatively low ratio. The gamma-globulins were estimated in 8 cases: in 4 cases these were totally or almost totally absent; in 2 the absolute values were very low; and in the remaining 2, of which our case was one, they were normal. The methods used in performing the qualitative and quantitative analyses are rarely mentioned. It is therefore impossible accurately to assess the figures given.

In brief it can be said that the most constant and most outstanding finding in this series of cases of hypoproteinaemia and oedema in the absence of primary insufficiency of dietary protein or proteinuria has been disturbance in pancreatic function. It is clear that, in addition to liver function tests, investigations of pancreatic function should be carried out in these children routinely even in the absence of classical signs of cystic fibrosis of the pancreas.

Summary

A child aged 4 months with pancreatic dysfunction, hypoproteinaemia, and oedema showed rapid improvement in the oedema and hypoproteinaemia following the institution of specific therapy. It is proposed that at least some of the cases of "idiopatic" hypoproteinaemia may be due to pancreatic dysfunction.

Hypoprotéïnémie idiopathique et hypoprotéïnémie par dysfonctionnement pancréatique.

Un nourrisson de 4 mois présentant une hypoprotéïnémie et des œdèmes par dysfonctionnement pancréatique a été rapidement amélioré par des enzymes d'origine pancréatique (Granules de Pantéric). Il est possible que certains cas considérés comme hypoprotéïnémie idiopathique soient en réalité provoqués par un dysfonctionnement pancréatique.

Idiopathische Hypoproteinämie oder Hypoproteinämie infolge Pankreasdysfunktion.

Ein 4 Monate alter männlicher Säugling mit Pankreasdysfunktion, Hypoproteinämie und Ödemen zeigte nach Behandlung mit Pankreasenzymen (Panteric granules) eine rasche Besserung der Ödeme und der Hypoproteinämie. Es wird angenommen, dass wenigstens einige der Fälle von „idiopathischer" Hypoproteinämie die Folge einer Pankreasdysfunktion sind.

Hipoproteinemia idiopática frente a lá debida a insuficiencia pancreática.

Un lactante, varón de 4 meses, afecto de disfunción pancreática, edema e hipoproteinemia, mostró rápida mejoría de estos dos últimos al administrarsele enzima pancreática (Pancreatic granules). Se sugiere que algunos casos de hipoproteinemia llamada idiopática puedan ser dedidos a disfunción pancreática.

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Renal Function in Infantile Obstructive Uropathy

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In cases with untreated bilateral hydronephrosis the disease terminates fatally within 10 years in two thirds of the patients due to gross renal damage with uremia (6). However, the available information concerning renal function during the early stages of obstructive uropathy in infancy and early childhood are sparse and incomplete. GROSS (10), and LAURET *et al.* (14) have stated that in the early course of the disease the patients might develop polyuria due to loss of the ability to excrete a concentrated urine and that at the same time there might be an elevated non-protein nitrogen level.

In this communication, some data will be presented which indicate that renal tubular damage resulting in a disturbance of electrolyte and acid-base regulation, as well as of the renal water reabsorption, might develop early in the course of congenital obstructive uropathy. As a consequence of these changes, such features as a failure to thrive or gastrointestinal symptoms such as vomiting might develop as the initial symptoms. Thus, the symptomatology might resemble that seen in infantile renal acidosis (16).

Although, as has been stated by CAMPBELL, chronic pyelitis is regularly found in bilateral hydronephrosis, the symptoms arising from the disturbed renal tubular function might, in some cases, be those calling attention to the primary disease. Due to the renal tubular defects, the infants suffering from obstructive uropathy might develop severe acidosis and dehydration in the course of a relatively mild gastro-enteritis, and there might be a lack of complete correction of the fluid and electrolyte imbalance following the acute stage.

Material

Six cases with obstructive uropathy have been studied. All patients, except one, showed symptoms of their disease during early infancy. A short account of the clinical course in each case will be given below.

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Case 1.—A boy, K. H. Birthweight 3,610 g. At an age of four days he had hematuria and a few days later urinary tract infection was diagnosed. During the following two weeks he had vomiting, diarrhoea and weight loss. At the age of 3 weeks he was admitted to the Pediatric Clinic, Karolinska Sjukhuset.

Examination on admission revealed a lethargic, dehydrated boy with a weight 600 g below birth weight. The distended bladder could be seen as a protrusion of the lower part of the abdominal wall. The left kidney was palpable. The micturition lacked force. There were 80 ml of residual urine. Urethral valves were suspected. N.P.N. 120 mg per 100 ml. Urethrocystography showed urethral valves below the verumontanum. The upper pouche of the bladder resembled a dilated urachus.

Treatment and progress: The patient was treated preoperatively for two weeks with an indwelling catheter and the fluid and electrolyte imbalance was corrected. A suprapubic operation with retrograde dilation of the urethra by sounds was then performed. There were no postoperative complications. I.v. urography showed bilateral hydronephrosis and poor excretion. There was a rapid fall in the N.P.N. level, which was only slightly elevated (56 mg per 100 ml) when the patient, at an age of 2 months, was discharged from the hospital. The following 2 months he was in fairly good condition and gained 2.5 kg in weight in 10 weeks.

At an age of four and one-half months he was readmitted because of severe dehydration and acidosis associated with acute gastro-enteritis. On admission, the N.P.N. level was relatively high (79 mg per 100 ml), but was normal within a few days after fluid and electrolyte therapy. He was hospitalized for two months and was found to have a moderate acidosis, also when he had recovered from the acute disease. During that period he had two more dyspeptic attacks followed by rapid dehydration. In both instances it was necessary to correct the fluid imbalance by the intravenous route. During the whole period there was pyuria. X-ray examination of the skeleton at an age of 6 months showed low mineralization of the type seen in acidosis.

Because of the persistant acidosis the patient was treated with sodium citrate, 2 g a day. After another 6 months the dose was reduced to 1 g per day. With this treatment the acid-base balance was corrected and the child developed normally. The child was last seen at the age of one and one-half years. At that time the weight was normal and the skeleton showed slight decalcification. Dilatation of the pelves and ureters had decreased, the excretion increased. N.P.N. normal. The pyuria persisted.

Case 2.—A boy, L. L. Birthweight 3,800 g. The child was breast-fed. He developed normally during the first 7 months. At that age he developed gastrointestinal symptoms with vomiting and diarrhoea and a few weeks later an infection of the urinary tract was diagnosed. Because of the suspicion of a malformation in the urinary tract he was admitted to the Pediatric Clinic, Karolinska Sjukhuset.

Physical examination on admission revealed an alert, normally developed, well-nourished 8-months-old boy with a weight of 7,700 g. There were no symptoms of dehydration.

Intravenous urography showed a marked impairment of the excretion from the right kidney and the renal pelvis was dilated. There probably also was an upper pelvis without excretion. The excretion from the left kidney was normal but the pelvis was slightly dilated. In the bladder a big ureterocele was visualized, which extended down into the urethra.

Treatment and progress: A suprapubic excision of the ureterocele was performed. There were no post-operative complications. Six weeks after the operation the patient had a mild pharyngitis complicated by intense vomiting causing severe dehydration.

Following this acute infection there was a persistent acidosis. Roentgenograms of the skeleton revealed low mineralization and multiple green-stick fractures. Because of the acidosis the patient was treated with sodium citrate, 3 g per day. Control examination 6 months later (at the age of 15 months) revealed a normally developed boy. X-ray examination of the skeleton showed normal mineralization, and there were no fractures. On urography, there was normal excretion from both kidneys but poor excretion from the right upper pelvis. There was less dilatation of the right lower pelvis than earlier.

Case 3.—Boy, S. K. Birthweight 3,110 g. The infant was breast-fed and thrived the first month of life. At the age of two months he had repeated infections of the respiratory tract and started to gain weight slowly. When three and one-half months old he was admitted to the Pediatric Clinic, Karolinska Sjukhuset, because of intense vomiting and diarrhoea.

Physical examination on admission revealed a moderately dehydrated, slightly malnourished infant in bad general condition. His weight was 4,700 g. There were symptoms of a urinary tract infection and the micturition lacked force. There was a moderate acidosis. Urography revealed bilateral hydronephrosis and hydroureters with normal excretion. Urethrocystography showed a dilatation of the posterior urethra and urethral valves below the verumontanum.

Treatment and progress: After correction of the fluid and electrolyte imbalance and after treatment of the urinary tract infection the infant was operated upon. A cystotomy and a retrograde dilatation of the urethra by sounds was performed. There were no post-operative complications. After the operation the patient developed normally and gained weight in a normal way. There were no gastrointestinal symptoms. The patient was last seen at the age of one year. Urography at that time showed regression of the hydronephroses.

Case 4.—Boy, N. S. Birthweight 4,200 g. The patient progressed well until the age of 9 months when he developed an acute suppurative otitis. During the following months he had anorexia and failed to thrive. At the age of one year he had polydypsia and polyuria. These symptoms increased in intensity and at an age of 15 months he was admitted to a community hospital because of anorexia, vomiting and irritability. The patient was found to have an infection of the urinary tract, and urography showed bilateral hydronephrosis. Because of these findings the child was referred to the Pediatric Clinic, Karolinska Sjukhuset.

Examination on admission revealed a thin, 16-months-old boy with a weight of 10 kg. Urography showed bilateral hydronephrosis with reduced excretion. Urethrocystography revealed urethral valves below the verumontanum. Roentgen examination of the skeleton was normal.

Treatment and progress: A transurethral resection of the valves was performed. There were no post-operative complications. Because of persistent acidosis the patient was treated with sodium citrate, 2 g per day. After operation and treatment with alkali the patient was in good condition and gained one and a half kg in weight in 4 months. His thirst decreased, but a moderate polyuria remained. When alkali therapy was omitted, acidosis returned. The patient was last seen 6 months after the operation (at an age of almost 2 years). At that time urography showed improved excretion and regression of the dilatation.

Case 5.—J. L. Birthweight 3,220 g. Normal development. Since seven months of age periods of fever and abdominal pain. With these attacks there was observed a

mass, the size of an orange, in the right side of the abdomen. Hematuria on one occasion. Referred to the Pediatric Clinic, Karolinska Sjukhuset.

On admission he seemed to be in good general condition. Weight 10 kg. Micturition normal. The examination revealed an enormous hydronephrosis on the right side, due to ureteropelvic obstruction. There was no roentgenologically demonstrable excretion. On the left side a moderate hydronephrosis with normal excretion was present. Because of acute retention in the hydronephrosis on the right side a pyelostomy was performed. Later, operation of the left hydronephrosis, and then a right-sided nephrectomy.

Case 6.—Boy, L. L. The patient was admitted to the Pediatric Clinic, Karolinska Sjukhuset, at the age of three years because of bilateral hydronephrosis. The symptoms of the disorder had started one year earlier with an infection of the urinary tract.

Examination on admission revealed an alert, normally developed boy with an infection of the urinary tract. Urography showed impairment of the excretion from the left kidney but a normal excretion from the right one. There were bilateral hydronephrosis with a marked dilatation of the left pelvis and a moderate dilatation on the right side. Urethrocystography revealed a marked dilatation of the posterior urethra possibly caused by valves below the verumontanum. There was no impairment of electrolyte balance.

Treatment and progress: A transurethral resection of the valves was performed. There were no post-operative complications. On reexamination, 6 months after the operation, there was no disturbance of renal function. Skeletal roentgenograms were normal.

Summary of the clinical findings in the patients studied

All six patients with obstructive uropathy were males. In five of the patients the symptoms had started during infancy. In one of the children the obstruction was caused by a ureterocele, in one case by uretero-pelvic obstruction, in four by urethral valves. Impairment of renal function, as revealed by urography, was found in five of the patients. In the same patients, evidence of damage to the renal tubular function was also demonstrated by the presence of acidosis or polyuria. Although there was, in some of the patients, a considerable improvement in renal function after operation, no complete restitution was obtained. In none of the children was there progress of the kidney damage after operation.

Studies of the Renal Function

Methods

General technique.—Urine for the determination of pH and carbon dioxide combining power was obtained by catheterization; the urine was collected under a layer of mineral oil. For the determination of the daily ammonia production in the kidneys, the patients were continuously catheterized and the urine was collected under mineral oil in a bottle which was chilled by ice-water and which contained a few ml of toluene.

Analythical methods.—Sodium and potassium in serum and urine were determined with a Beckman flame-photometer, and the total base in blood serum with a Philips

Conductivity Measuring Bridge GM 4249. Chloride values in serum and urine were obtained by a modification (4) of the method of SCHALES and SCHALES (21). Urine calcium was determined according to KRAMER and TISDALL (13), and in serum according to BIERING (3). Urine and serum phosphate was estimated by the method of YOUNGBERG and YOUNGBERG (24). The N.P.N. was estimated after Nesslerization.

The pH of blood and urine was determined with a Beckman pH meter. The carbon dioxide combining power of blood serum and urine was determined partly by the manometric method of VAN SLYKE and NEILL (23), partly by the titration method of VAN SLYKE (22). The ammonia content of urine was determined by the method described by FOLIN and BELL (7). Alkaline phosphatase activity in serum was determined according to BUSCH and BUSCH (5). With this method the upper normal limit during the first few years of life is about 16 units per 100 ml serum.

Results

In none of the patients studied was a complete investigation of the renal function performed. The results which are summarized in Tables 1–4 and Figures 1–2, seem, however, to permit the following conclusions regarding the nature of the renal damage which develops in obstructive uropathy.

Defective acid-base regulation.—In all patients, except Cases 5 and 6, there was a low serum carbon dioxide combining power, although the pH was within the normal range (Cases 1 and 2). The roentgenological examination of the skeleton in Case 1 and Case 2 showed a low mineralization and the same features as those found in the Milkman syndrome, a disorder with a decalcification of the skeleton caused by an impairment of the reabsorption of fixed base by the kidney tubules, cf. ALBRIGHT & REIFENSTEIN (2).

In Case 3 and Case 4 there was a heavy urinary loss of bicarbonate despite a decreased serum carbon dioxide combining power (Table 2); in Case 4 the carbon dioxide combining power in the urine was 4.5 mEq per liter at the same time as it was 19.3 mEq per liter in the serum, and in Case 3, after a load of calcium chloride, there was only a slow decrease of the bicarbonate concentration in the urine and no increase of the ammonia excretion (Table 3). For normal values of carbon dioxide combining power of urine cf. GAMBLE (8).

As was demonstrated in Case 5 (Table 2), there might be differences between both kidneys with regard to their capacity to conserve base. In this patient, there were bilateral hydronephrosis, but as was revealed from the urography, the excretion from the right kidney was more impaired than from the left. When a nephrostomy had been performed on the right side it was possible to collect urine from each kidney separately. As was expected, the carbon dioxide combining power was found to be higher in the urine from the right kidney than in that from the left. The urine from the right kidney also showed a higher pH.

TABLE 1

Blood chemistry in the patients studied.

In the first four patients, a moderate to severe acidosis was present before operation. The N.P.N. was definitely increased only in Case I.

	Total base mEq/l.	Sodium mEq/l.	Potassium mEq/l.	Chloride mEq/l.	Bicarbonate mEq/l.	pH	Calcium mg per 100 ml	Phosphate mg per 100 ml	Alkaline phase Busch-U. per 100 ml	N.P.N. mg per 100 ml
Case 1										
On admission . . .	—	—	—	109	—	—	—	—	—	120
Before op., during dyspepsia . . .	—	—	—	83	8.0–18.1	—	—	—	—	79
After op. and correction with sodium citrate . .	148	136	3.3	99	28.0	7.45	8.0	4.9	19	38
Case 2										
6 weeks after operation	169	—	—	99	19.2	7.46	10.2	7.6	22.5	36
Case 3										
On admission . . .	—	138	—	94.5	12.0	—	—	—	—	40–44
2 weeks later, after correction of electrolyte imbalance .	—	142	4.7	111	26.0	—	—	7.3	16	—
Case 4										
On admission . . .	—	—	—	100	19.0	—	10.0	6.3	10	48–35–19
After operation . .	—	147	5.8	109	19.3	—	11.4	7.7	18	43–41
6 months after operation	—	158	—	109	19.0	—	11.1	8.3	—	44
Case 5										
After pyelostomy .	—	134	3.7	122–100	24.0	—	11.1	6.8	13	35
Case 6										
Before operation .	—	139	5.1	102	24.0	—	9.8	8.2–5.7	7	42–25

Defective tubular function as revealed from the excretion of water and solutes. —In Case 4, there was a polyuria with an average daily urinary output of 700–800 ml, with an upper value of 1,300 ml. As was demonstrated by a thirst test followed by a water load (Fig. 1), there was in this patient a hypostenuria. The incapability to increase the reabsorption of water in the kidney tubules was also shown by a pitressin test (Fig. 2). Besides polyuria,

TABLE 2

Urinary acid-base regulation and skeletal X-ray in the patients studied.

In Cases 3 and 4, there was a definitely increased total CO_2 content of urine. In Case 5, bicarbonate reabsorption seems to be less efficient in the kidney with uretero-pelvic obstruction. In Cases 1 and 2, there was decalcification of the skeleton, indicating a long-standing acidosis. Calcium excretion normal or low.

	Calcium mg per 24 h	Total carbon dioxide combining power simultaneously determined		pH of urine	Skeletal X-ray
		in blood serum mMol/l.	in urine mMol/l.		
Case 1					
Before operation . .	—	—	—	—	5 months after operation: decalcification. After treatment with sodium citrate: normal.
After operation, during dyspepsia . .	—	13.1	—	5.5	
Case 2					
6 weeks after operation	5.6	19.2	—	6	Decalcification, green-stick fractures. After sodium citrate for 6 months: normal.
Case 3					
Before operation . .	5.0	—	17.5	7.05	Normal
Case 4					
Before operation . .	19.0	19.3	4.5	6.5	Normal
After operation . .	23.0	—	—	—	
Case 5					
After operation					
Pyelostomy	7.6	22.9	6.1	7.25	Normal
Bladder	28.8		2.9	6.4	
Case 6					
Before operation . .	—	—	—	—	
After operation . .	—	—	2.1	5.55	Normal

TABLE 3

Response to acid load in Case 3 before operation.

Duration of Period I, 24 hours; duration of Periods II and III, 12 hours. During Period II, administration of 2.5 g of calcium chloride, divided in five doses at equal intervals. Bicarbonate is given in mEq/l., ammonia in mg N, other values in mg. Excretion of bicarbonate was decreased very slowly. There was no increase in ammonia production.

Period number	I	II	III
Collecting time (hours)	24	12	12
Urine vol. (ml)	200	120	170
pH	7.05	6.90	6.60
CO_2 comb. power	17.5	10.1	7.3
Sodium	70	20	20
Potassium	320	180	180
Calcium	5	4	9
Chlorides	105	133	203
Ammonia	232	96	126

TABLE 4

The concentration of different solutes in bladder and pyelostomy urine in three 24-hour samples in Case 5.

Values given in mg per 100 ml. The high bladder/pyelostomy quotient indicates poor tubular reabsorption of water in nephrostomic kidney.

	Urine from the bladder					Urine from the pyelostomy					Quotient Bladder/Pyelostomy				
	Cl	Na	K	Ca	P	Cl	Na	K	Ca	P	Cl	Na	K	Ca	P
1. .	548	284	95	9.1	180	217	161	68	1.7	40	2.5	1.8	1.4	5.4	4.5
2. .	714	480	162	13.1	124	294	209	54	3.3	29	2.4	2.3	3.0	4.0	4.3
3. .	555	340	238	18.0	202	217	145	57	5.6	40	2.6	2.3	4.2	3.2	5.1

there was also a persistent acidosis and the patient required for its correction continuous treatment with alkali, even after operation.

From the studies of the output of solutes and the urine volume in the patient with a nephrostomy on the right side (Case 5), no definite damage to the tubular function of the left kidney could be demonstrated (Table 4). The same studies of the function of the right kidney showed, however, that there was a marked depression of the tubular reabsorption of water.

Other tests of renal function.—No studies of the glomerular filtration rate or of the renal plasma flow were performed. As is shown in Table 1, the N.P.N. level was normal or slightly elevated during the whole period of ob-

servation unless in association with severe dehydration and acidosis (Case 1). This finding, and the observation that there was no increase in the serum phosphate concentration, points out that there was no gross damage to glomerular filtration, i.e. the G.F.R. was more than 25 ml per minute (9).

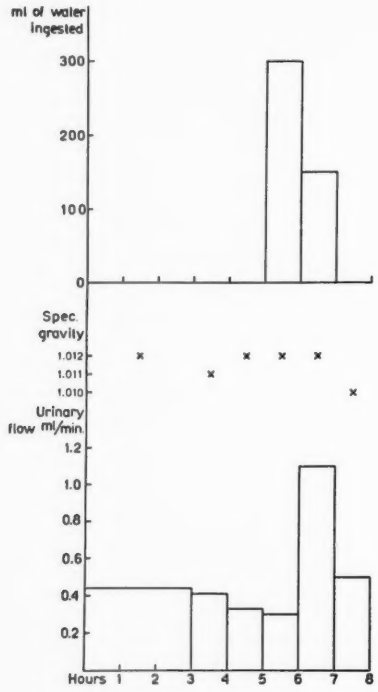

Fig. 1. Thirst test, Case 4. Before the test the patient had been thirsting for 13 hours. Upper section of figure shows the amount of water ingested during the experiment; lower section, urinary flow/min. and specific gravity of each specimen. Concentration and dilution power were impaired.

Data concerning renal function obtained from urographic examinations are summarized in Table 5. From these investigations it is clear that there was an impairment of the tubular excretion capacity in several patients, but also that an improvement often was observed after operation. Fig. 3 shows the urography before and after operation in a patient with obstructive uropathy (Case 3). The figure clearly demonstrates the improvement after operation.

Comment

From the studies of renal function in the cases above it is obvious that in congenital low urinary tract obstruction, kidney damage may be present even in early infancy. This is due to the fact that kidney excretion starts in the fourth to fifth fetal month (12) and consequently hydronephross may be developed at birth, making the patient susceptible to infection.

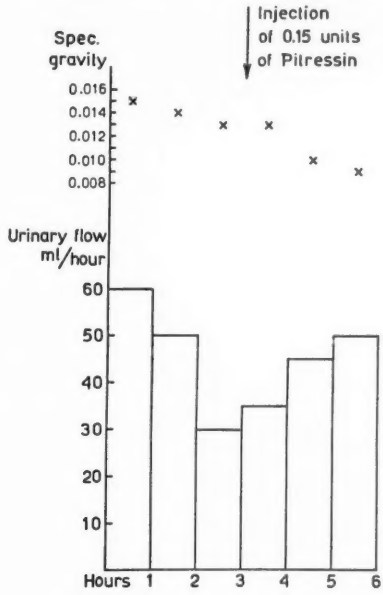

Fig. 2. Pitressin test, Case 4. The patient was hydrated during the entire experiment. At arrow, injection of 0.15 units of Pitressin. No antidiuretic effect was observed.

The characteristics of the failure which develops are those found when there is an impairment of renal tubular function. In none of the patients studied was there definite evidence of glomerular insufficiency. The finding that out of 6 patients only one failed to reveal any abnormalities points out the high frequency of renal failure in obstructive uropathy in childhood. The symptoms which develop from renal damage may be so pronounced that they might be obvious before any other symptoms of the primary disease are recognized.

The following findings indicate the presence of renal tubular failure: Urographic examination has revealed an impairment of the excretory capacity. In some of the patients chronic acidosis had developed which, in two

TABLE 5

Postoperative changes in hydronephroses and excretion capacity at i.v. urography.

Case No.	Dilatation	Excretion	Obs. time postoperatively
1	decreased	improved	18 months
2	decreased	normal	8 months
3	decreased	normal (as preoperatively)	6 months
4	decreased	improved	6 months
6	unchanged	unchanged	5 months

instances, had caused demineralization of the skeleton. Polyuria, which in the course of a mild infection might cause a severe dehydration, has also been observed. There was, in those patients, a tendency to hypostenuria.

Observations similar to those found in our patients have been noted also in other conditions. RETLEV-ABRAHAMSEN & AALKJAER (19) and AALKJAER 1943 (1) pointed out the frequency of dehydration and acidosis in prostatism. LICH (15) has shown that, in patients with the same condition, the phenol red clearance is much more reduced than the inulin clearance; a finding which indicates that the primary kidney damage falls on the tubules. ROUSSAK & OLEESKY (20) have described the occurrence of symptoms resembling those in diabetes insipidus as the initial manifestation of renal failure in the course of hydronephrosis caused by prostatic hypertrophy. The features were the same as in our fourth case, i.e., there was a pitressin resistant hypostenuria. The same renal tubular dysfunction was observed by ROUSSAK & OLEESKY in a case of multiple myeloma. By microdissection of the nephrons it was, in this case, possible to show that there were degenerative changes localized to the distal and collecting tubules. Thus, there is evidence that, in obstruction of the urinary tract, the primary kidney damage arises in the distal and collecting tubules. Such a suggestion also finds support from the observation that in our cases there was a defect in the mechanism for stabilizing the alkaline reserve of the body, a process which, according to modern concepts of acid base regulation, takes place in the same area, cf. PITTS (17).

The cause of renal failure in obstructive uropathy is still a matter of discussion as regards the relative importance of infection and increased intrarenal pressure. Increased hydrostatic pressure affects the flow of urine and blood (25). KERR (11) found in dogs with unilateral ureteral obstruction a decrease in effective renal plasma flow to about 25 per cent of normal.

Fig. 3 *A*. Case 3. I.v. urograph preop. ($\frac{1}{2}$ hpc).

In chronic pyelonephritis, RAASCHOU (18) found from studies of inulin, mannitol and diodrast clearances that the kidney damage was mainly localized to the renal tubules, thus to the same area as in our patients. CAMPBELL (6) feels that the cause of the renal failure in patients with obstruction of the urinary tract might be ascribed both to the high hydrostatic pressure and to the infection. It is obvious that damage to the kidneys by infection will be more severe when combined with obstruction. In our cases the renal failure has at least in some respects decreased when the obstruction was removed, even if the urinary tract infection persisted.

Fig. 3 *B*. Case 3. I. v. urography, 3 $\frac{1}{2}$ months postop. ($\frac{1}{2}$ hpc). Hydronephroses diminished.

The rapidity with which renal failure develops points out the necessity of early surgical intervention to prevent further progress and irreversible renal damage. The early diagnosis is, however, often difficult. The only initial symptom pointing to a disease of the urinary tract may be a decrease in the force of the urinary stream, which is not always observed. It must be stressed, however, that micturition difficulties are not invariably present, and consequently the absence of this symptom does not exclude congenital low urinary tract obstruction.

Summary

From clinical observations and studies of the renal function in six male infants and children with obstructive uropathy, the following conclusions may be summarized:

1. The initial symptoms of the disease might be slow weight-gain, anorexia, vomiting and diarrhoea, often in connection with dehydration, or can be more localized, such as urinary infection or abdominal mass drawing attention to the malformation. Pronounced obstruction due to urethral valves might occur despite normal micturition.

2. Impairment of the renal tubular function might develop early in the course of the disease, long before there are any symptoms of glomerular damage as indicated from an elevated N.P.N. level. There was in four of the patients a moderate acidosis due to impairment of the capability to conserve fixed base. In one of the children, Pitressin-resistent polyuria with hypostenuria was demonstrated, and in another patient with unilateral ureteral obstruction there was an impairment of the water reabsorption in the hydronephrotic kidney.

3. After operation, there was a marked decrease in the hydronephrotic dilatation and improvement of the excretory capacity as revealed by radiologic examination. Although there were indications of improved renal tubular function after operation, polyuria and acidosis, requiring alkaline therapy, persisted in some of the patients during the period of observation.

4. The rapidity with which renal failure develops points out the necessity of early diagnosis and surgical treatment to prevent further progress and irreversible renal damage.

La fonction rénale dans les obstructions de l'appareil urinaire chez l'enfant.

De l'observation clinique et de l'étude de la fonction rénale chez six nourrissons et enfants masculins présentant une obstruction de l'appareil urinaire on peut conclure brièvement comme suit : Les premiers symptômes de la maladie peuvent être une augmentation lente du poids, de l'anorexie, des vomissements et de la diarrhée, qui sont souvent en relation avec une déshydratation. Ces symptômes peuvent être plus localisés comme une infection urinaire ou une masse abdominale attirant l'attention sur la malformation. Il peut exister une obstruction importante, malgré une miction normale, due à des formations valvulaires urétrales. Une atteinte de la fonction tubulaire rénale peut se développer précocement dans l'évolution de la maladie, longtemps avant que n'existent des symptômes de lésion glomérulaire, ainsi que le montre le taux élevé de l'azote non protéique. Quatre patients présentainet une acidose modérée due à une capacité réduite de conserver les bases fixées. Chez un enfant on a pu mettre en évidence une polyurie résistante à la pitressine avec une hyposthenurie, tandis qu'un autre patient souffrant d'une obstruction urétérale unilatérale présentait une diminution de la réabsorption d'eau au niveau d'un rein hydronéphrotique. Après l'opération la dilatation par hydronéphrose avait considérablement diminué et la capacité d'excrétion, ainsi qu'il a été découvert par l'examen radiologique, s'était améliorée. Quoiqu'on ait trouvé après opération des signes d'une amélioration de la fonction rénale tubulaire, la polyurie et l'acidose persistaient, obligeant à recourir à un traitement alcalinisant chez certains pendant la période d'observation. La rapidité avec laquelle l'insuffisance rénale se développe, démontre la nécessité d'un diagnostic et d'un traitement chirurgical précoce afin de prévenir une progression ultérieure et des lésions rénales irréversibles.

Die Nierenfunktion bei kindlicher obstruktiver Uropathie.

Aus klinischen Beobachtungen und Untersuchungen der Nierenfunktion bei sechs männlichen Säuglingen und Kindern mit obstruktiver Uropathie können folgende Ergebnisse zusammengefasst werden: Die initialen Symptome der Erkrankung können sein: träge Gewichtszunahme, Appetitlosigkeit, Erbrechen und Durchfall, oft in Verbindung mit Dehydration, oder sie können mehr lokalisiert sein wie eine Infektion der Harnwege oder ein Tumor im Abdomen, der die Aufmerksamkeit auf die Missbildung lenkt. Selbst bei normaler Miktion kann eine ausgesprochene Obstruktion als Folge von Urethralklappen vorkommen. Eine Beeinträchtigung der tubulären Nierenfunktion kann sich im Laufe dieser Erkrankung frühzeitig entwickeln, lange bevor irgendwelche Symptome eines glomerulären Schadens, angezeigt durch einen erhöhten Reststickstoffwert, vorhanden sind. Bei vier der Patienten bestand eine mässige Acidose, bedingt durch die Beeinträchtigung der Fähigkeit feste Basen zu erhalten. Das eine der Kinder zeigte eine Pitressin-resistente Polyurie mit Hypostenurie und bei einem anderen Patienten mit einseitiger Ureterstenose bestand eine Beeinträchtigung der Wasserrückresorption in der hydronephrotischen Niere. Nach der Operation zeigte sich eine merkliche Verringerung der hydronephrotischen Dilatation und eine Besserung der Ausscheidungsfähigkeit, wie durch röntgenologische Untersuchung festgestellt wurde. Obgleich nach der Operation Anzeichen einer gebesserten tubulären Nierenfunktion vorhanden waren, bestanden bei einigen der Patienten Polyurie und Acidose, die während der Beobachtungszeit alkalische Therapie erforderten. Die Schnelligkeit, mit der sich eine Niereninsuffizienz entwickelt, weist auf die Notwendigkeit einer frühzeitigen Diagnose und chirurgischer Behandlung hin, um einen irreversiblen Nierenschaden zu verhindern.

La funcion renal en las uropatías obstructivas del niño.

Del estudio clínico y de la función renal de seis lactantes y niños con uropatía obstructiva se pueden resumir las siguientes conclusiónes: Los síntomas iniciales de la enfermedad pueden ser aumento lento de peso, anorexia, vómitos y diarrea a menudo en relación con deshidratación, o mas localizados como infección urinaria o masa abdominal que dirija la atención hacia la malformación. Coexistiendo con una micción normal, puede haber una obstrucción pronunciada debida a válvulas uretrales. Mucho antes que la lesión glomerular aparezca, puede existir daño tubular como lo demuestra la elevación del nitrógeno no proteico. Cuatro pacientes presentaron moderada acidosis debida a reducción de la capacidad de conservar bases fijas. En un caso se demostró una poliuria con hipostenuria pitresín resistente. Otro, con una obstrucción ureteral unilateral, presentó una disminución de la absorción de agua a nivel del riñón hidronefrótico. Después de la operación, la dilatación hidronefrótica disminuyó considerablemente como lo mostró la radiografía y la capacidad de excreción aumentó. Aunque después de la operación hubo signos indicando mejoría de la función renal, en algunos pacientes persistieron poliuria y acidosis que requirieron terapéutica alcalinizante durante el período de observación. La rapidez con que se instala la insuficiencia renal demuestra la necesidad de un tratamiento y diagnóstico tempranos a fin de prevenir progresión de las lesiones y daño renal irreversible.

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From the Pediatric Clinic of the University of Uppsala
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Hereditary Cataract in Two Families

by RAGNA DAHLBERG PARROW

Cataracts can be congenital or developed postnatally. The congenital cataract can occur with other malformations, but it can also be isolated. It is usually due to hereditary factors, but it can also be caused by an injury during the first foetal months from X-rays or a rubella infection in the mother. In the case of the postnatal cataract a number of other causes, such as trauma, uveitis, poisoning, undernourishment and tetany have been reported (SAUTTER 1951). The manifestation of the genetic factor can sometimes be influenced by the environment (SORSBY 1955).

From reports of the Swedish Institute for the Blind at Tomteboda it appears that cataract is a common cause of reduction of sight in children. During the school year 1952–53, 142 patients were cared for, of whom 18 had hereditary and 7 had acquired cataracts. The hereditary cataracts usually follow a dominant inheritance trait (WAARDENBURG 1932), but recessive heredity and sex-linked heredity have also been established in a number of cases (GATES 1946, SAEBO 1949, GIANFERRARI 1954).

According to size and appearance cataracts are divided into different types. The cataract can be total or partial, and the latter, in turn, has many forms, the commonest of which are *cataracta zonularis*, *polaris*, *centralis*, and *suture cataract*. The hereditary cataract's clinical type is often constant for several generations, but in recent years many cases have been published in which the type has varied within the same family (NORDMANN 1954). The same holds true for the time of the cataract's appearance (SORSBY 1951). Thus, it cannot be determined by the cataract's clinical type whether it is hereditary or acquired. Injuries from X-ray or rubella most often give bilateral total cataracts, but the same clinical picture may also appear in the true hereditary forms. Cloudiness in the embryonic nucleus of the lens for the most part is due to dominant inheritance, while zonular cataracts may have several causes (SAUTTER 1951).

The following is a report of two cases of cataracts, in one case, congenital, in the other, early postnatal.

Case 1.—A. L., boy born on the 28th of March, 1946, in *partus normalis*. The mother was healthy during pregnancy. The patient had a congenital bilateral cataract, but no other malformations. He has been treated three times at the children's clinic for feeding trouble and neurotic reactions.

The cataract is of the central and dense type and was operated with discission twice during the years 1948–49. In 1954 the acuity of vision was Right (+ 16) = finger counting 2 meters, Left (+ 16) = 0.1.

Heredity: The patient's father, paternal grandfather and paternal uncle were born with cataracts in both eyes. The mother's family has had no history of cataracts for four generations. See Fig. 1.

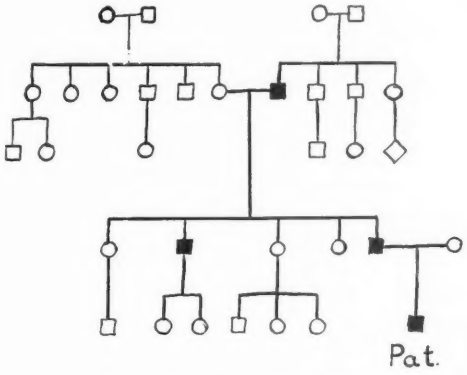

Fig. 1. Pedigree of family L.

Case 2.—E. R., boy born on the 21st of December, 1954, by a caesarian section. The mother was healthy during pregnancy until the 15th of November, when hypertonia and albuminuria were found. She was treated from the 20th of November under the diagnosis of toxicosis in pregnancy. There was no rubella in her history. She received various drugs to lower the blood pressure and to relieve pain during the time of treatment.

The birth occurred one week early. The child's weight at birth was 2,080 grams. The child was pale and asphyxiated at birth and was given oxygen by stomach tube and was transferred later on to the children's clinic. He lay in an incubator until the 5th of January 1955, but received oxygen only during the first 24 hours.

The patient received breast milk with an additional supply of acid full milk and vitamins in the form of AD-drops and ascorbic acid. The general condition was satisfactory, and the weight gain progressed in a normal manner.

Ophthalmoscopic control was first performed on December 29, 1954, without any pathological findings being observed. At the second ophthalmoscopic control on Jan. 24, 1955, a bilateral clouding of the lens was discovered, which was moderately dense and central with a sharp boundary. Diagnosis: *Cataracta nuclearis oc. amb.* Renewed control on Febr. 7, 1955, showed essentially the same findings.

The patient had a mild anemia and was sent home with AD vitamins and an iron preparation.

On the 11th of March, 1955, the patient came in again to be under hospital treat-

ment. Eye examination showed that the process had continued to complete cloudiness of both lenses. Diagnosis: *Cataracta totalis oc. amb.*

Heredity: Three cousins and the child of one cousin to the father were born with cataracts. The father's brothers and sisters, parents and maternal grandparents have no cataracts. The patient's mother has no cataracts in her family. She has three healthy children from an earlier marriage. See Fig. 2.

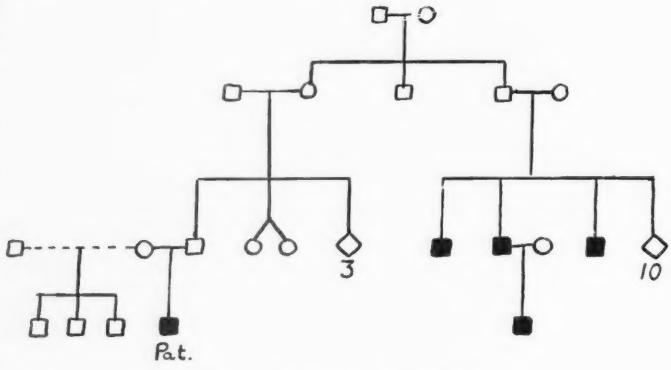

Fig. 2. Pedigree of family R.

Discussion

Case 1 concerns, doubtlessly, a hereditary cataract which at first seems to be dominant. Under such conditions, however, it is strange that the paternal grandfather's brothers and sisters are healthy. That could be due to the fact that the trait occurred as a mutation in the paternal grandfather. The four cases in the L. family are all men, and there are possibilities of sex-linked heredity. The number of children in the two last generations is too small to show anything definite in this respect, but the possibility cannot be excluded.

From the pedigree of Case 2 it appears that there cannot be a question of a dominant trait or a sex-linked one. A recessive inheritance is of course possible even if inbreeding does not occur in the family, and one must therefore assume that three outside heterozygotes for just that factor have been bred into the family. Irregular dominant inheritance is not likely, even if the tendency should have weak penetration.

If the cataract in Case 2 is looked upon as a separate entity, the other cases in the family may be explained by a recessive factor (possibly sex-linked). The possibility that the patient has an acquired cataract cannot be excluded even if the coincidense is striking and no obvious reasons like tetany, undernourishment and uveitis are known. The mother was healthy

in the beginning of her pregnancy, but later developed a toxicosis, the effect of which upon the child is difficult to state. This is also the case with the child's immaturity. GUY (1954) has published a couple of cases of premature babies who had progressive bilateral cataracts during the first year of life without any hereditary or clinical explanations having been found. One or more other factors can be the cause, but the possibility of an hereditary form is present, and it would in this case be recessive. The cataract is possibly due to the interplay between a hereditary tendency and environmental factors.

The prognosis of a cataract is due not so much to the origin as to the clinical picture. The cataract's type and the occurrence of other malformations in the eye are of fundamental importance. A polar cataract gives few symptoms, and a small central cloudiness can sometimes be treated with atropine when a broad peripheral zone of the lens is clear. The total cataract has the worst prognosis, even after operation, especially if nystagmus occurs simultaneously. The patients described above are both operation cases. Case 1 has already undergone operation and cannot be expected to attain better acuity of vision through further measures. Case 2 should undergo operation around one year's age and then receive correction for his aphakia. The late result of the operation is the same whether the operation occurs before one year's age or between one and three years (BRÆNDSTRUP 1943). Before one year, however, the risk of complications is greater (synechies, pupil displacement, etc.).

Summary

Two cases of cataract in infants have been presented. In one case the origin is definitely hereditary, in the other it seems possible that it is a question of an interplay between hereditary and environmental factors.

Cataracte héréditaire dans deux familles.

L'auteur présente deux cas de cataracte chez des nourrissons. Dans un cas elle avait une origine nettement héréditaire, tandis qu'il semble que pour l'autre des facteurs d'hérédité et d'environnement aient pu agir simultanément.

Erblicher Katarakt in zwei Familien.

Es werden zwei Fälle von Katarakt bei Kindern beschrieben. In einem Fall ist die erbliche Genese klar, in dem anderen scheint ein Zusammenspiel zwischen erblichen und äusseren Faktoren vorzuliegen.

Cataratas hereditaria en dos familias.

El autor presenta dos casos de catarata en lactantes. En un caso el origen era francamente hereditario, mientras en el otro los factores hereditarios y ambientales parecían combinarse.

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Coeliac Disease. V

Some Experiments on the Cause of the Harmful Effect of Wheat Gliadin

(*Preliminary communication*)

by J. H. VAN DE KAMER and H. A. WEIJERS

In preceding investigations it was demonstrated that especially wheat flour exerts a harmful influence on coeliac patients, causing anorexia, vomiting, apathy, diarrhoea and steatorrhoea. The protein fraction of the wheat, in particular gliadin, proved to be the responsible factor (1). Therefore it was concluded that the cause of the patient's troubles, when eating wheat, must be primarily sought in the metabolism of the wheat protein, the steatorrhoea being considered a secondary phenomenon. In order to study the deleterious effect of gliadin, this substance may be separated into various fractions, either physico-chemically, in which the protein as such remains intact, or by means of enzymes or chemicals, by which it is completely or partially broken down. The chemical method is chosen rather than the physico-chemical procedure, in view of the abnormal amino-acid composition of gliadin, which has very low contents of lysine, methionine, threonine and other amino-acids, and an abundance of glutamine (the monoamide of glutamic acid).

It is highly improbable that the (harmful) effect of gliadin is caused by the *lack* of any amino-acid, since a diet rich in milk proteins does not protect coeliac patients against the bad influence of wheat. Therefore, the investigation was especially focussed on the glutamine, which is present in gliadin in an abnormally high proportion (43 %).

First, two 6-year-old coeliac patients, who were in good condition and who received a wheat-free diet, were given glutamine by mouth for a period of six weeks, in doses increasing from 2 to 4 g daily (this corresponds with 125—250 g of wheat flour). No reaction was, however, observed, either clinically or chemically. This observation proved that glutamine in the form

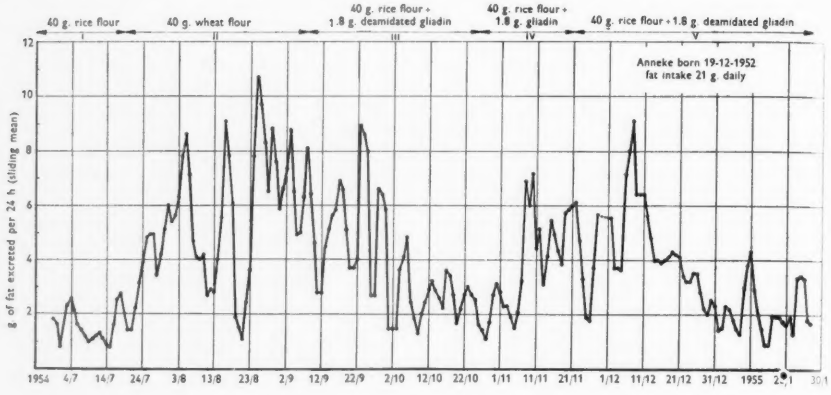
40 g. rice flour
40 g. wheat flour
40 g. rice flour + 1.8 g. deamidated gliadin
40 g. rice flour + 1.8 g. gliadin
40 g. rice flour + 1.8 g. deamidated gliadin
I
II
III
IV
V
Anneke born 19-12-1952
fat intake 21 g. daily
g of fat excreted per 24 h (sliding mean)
12
10
8
6
4
2
1954 4/7 14/7 24/7 3/8 13/8 23/8 2/9 12/9 22/9 2/10 12/10 22/10 1/11 11/11 21/11 1/12 11/12 21/12 31/12 1955 30/1

Fig. 1. Excretion of fat in faeces of a coeliac patient on diets containing daily 40 g rice flour, wheat flour or rice flour with 1.8 g gliadin or gliadin, 90 % deamidated.

of a *free* amino-acid is not the toxic substance loooked for. It is, however, not impossible that glutamine *bound in protein* does indeed exert a harmful influence.

Gliadin was therefore treated chemically in such a way that it remained intact as a protein, while the glutamine was decomposed by a process of deamidation. This can approximately be brought about by hydrolysing gliadin by boiling it with 1*N* HCl for 45 minutes. In this way 90 % of the glutamine is dissociated into glutamic acid and ammonia, the peptide bonds being affected to only a slight degree, so that the protein nature of the gliadin is preserved.

Roughly speaking, this procedure therefore yields a protein with the same amino-acid composition as gliadin, but containing glutamic *acid* instead of glutamine. The ammonia liberated remains in solution as ammonium chloride.

This deamidated gliadin was given during three separate periods to two coeliac patients who had clearly exhibited the toxic effect of wheat diet.

After the substitution of gliadin by the equivalent amount of deamidated gliadin, one patient, a girl $1\frac{1}{2}$ years of age (Fig. 1) completely recovered on both occasions. She became active again, her appetite became normal, pallor and abdominal pain disappeared, as did the diarrhoea. The steatorrhoea, an objective criterion, also decreased, as is shown in the figure.

The second patient, a boy of about 8 years, was a very severe case of coeliac disease; this was demonstrated not only by the clinical reaction to wheat, but also by the severity of the steatorrhoea. At first this patient also showed a considerable clinical improvement when the gliadin was

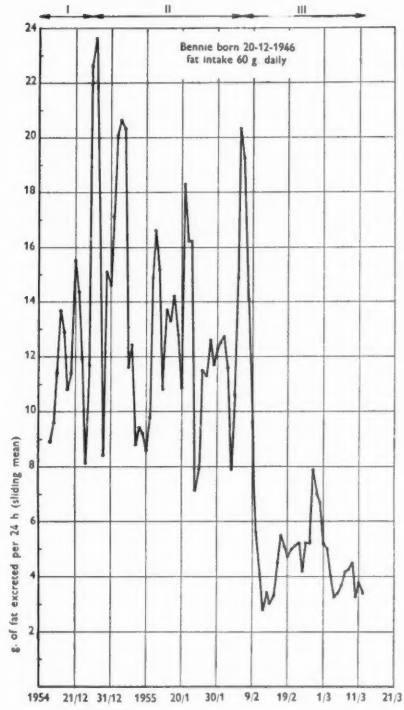

Fig. 2. Excretion of fat in faeces of a coeliac patient on diets containing daily 200 g of buckwheat bread and 4 g gliadin (period I), 4 g gliadin 90 % deamidated (period II) and 4 g gliadin 97 % deamidated (period III).

replaced by its deamidated form; but the improvement did not persist, and the steatorrhoea did not decrease either (Fig. 2, periods I and II).

The possibility was therefore considered that the residual 10 % glutamine in the gliadin which is not hydrolysed into glutamic acid would still be too much for this seriously ill patient. The deamidated gliadin of his diet was therefore substituted by gliadin which was still further deamidated to such a degree that only 3 % of unchanged glutamine was left. The clinical improvement was clear now and the steatorrhoea decreased sharply (Fig. 2, period III).

The preparation is just the same as for the first form of deamidated gliadin, except that it was boiled with 1*N* HCl for *two* hours instead of 45 minutes. By this treatment the protein is slightly more affected, about 15 % of the peptide bonds being hydrolysed.

The above experiments show that gliadin becomes harmless for coeliac patients if it has been boiled with 1*N* HCl for a short time. Because the most important change brought about by this treatment in the gliadin molecule is the conversion of glutamine into glutamic acid, it may be taken as a working hypothesis that glutamine, bound in gliadin – but not as a free amino-acid – is responsible for the effect described.

If our working hypothesis is right, a division into harmless and harmful proteins according to their amid-nitrogen content must be possible. To examine this the ratio amid-nitrogen/non-amid-nitrogen of several foodstuffs was determined. To establish these ratios the ammonia liberated by boiling for 4 hours with 1*N* HCl was related to the total NH_3 set free by a normal Kjeldahl treatment (see Table 1).

TABLE 1

Ratio amid-nitrogen/non-amid-nitrogen in different foodstuffs.

Foodstuffs	$\frac{\text{amid N}}{\text{total N} - \text{amid N}} \times 100$	Foodstuffs	$\frac{\text{amid N}}{\text{total N} - \text{amid N}} \times 100$
beefsteak	6	rice	11
cod	7	maize	11
egg white protein	7	oat flakes	12
potato protein	7	oats	13
green peas	8	barley flour	14
buckwheat	8	rye flour	17
brown beans	9	glutenin	22
soybean-oil meal	10	wheat flour	23
whole egg	11	gluten	27
casein	11	gliadin	30

In this list all the proteins that are harmless have amid-nitrogen figures of 11 or less whereas all those proteins which are harmful have higher values, especially gluten and gliadin. These findings support our working hypothesis.

Asparagine also contains amid-nitrogen. It is not excluded therefore by the above experiments that not glutamine – or not only glutamine – but asparagine in bound form exerts a harmful influence. Since in gliadin asparagine is only present in slight amounts in comparison to glutamine, we have not made in our experiments a distinction between glutamine and asparagine.

From the clinical side we are encouraged by finding still further support by having observed that when a really severe coeliac patient was given the same amount of gliadin, gluten and glutenin, having amid-nitrogen figures of 30, 27 and 22 respectively, the clinical reactions were clearly differentiated as very severe, severe and only mild.

Summary

The harmful effect of gliadin (containing 43 % glutamine) in coeliac patients can be abolished by a mild treatment of this substance with HCl. Since glutamine as such has no harmful influence, it is accepted as a working hypothesis that glutamine in bound form is the cause of the deleterious effect of wheat.

It appeared that foodstuffs having a high ratio amid-nitrogen/non-amid-nitrogen are deleterious, whereas foodstuffs having a low ratio are harmless. In a number of foodstuffs this ratio has been determined.

Malade cœliaque : V. *Quelques expériences sur la cause de l'effet nocif de la gliadine du froment.*

On peut abolir chez des patients atteints de maladie cœliaque l'effet nocif de la gliadine (qui contient 43 % de glutamine) en laissant agir l'acide chlorhydrique légèrement sur cette substance. La glutamine comme telle n'ayant pas d'influence nocive, on a admis comme hypothèse valable que la glutamine dans sa forme liée est la cause de l'effet nuisible du froment. Il a semblé que des aliments contenant un rapport élevé : azote-sous-forme-d'amide/azote-sous-forme-non-amide sont nuisibles, tandis que des aliments ayant un rapport abaissé sont inoffensifs. Ce rapport a été déterminé pour un certain nombre d'aliments.

Coeliakie. V. Einige Untersuchungen über den schädlichen Einfluss von Weizengliadin.

Der nachteilige Effekt von Gliadin (das 43 % Glutamin enthält) bei Coeliakie-Patienten kann durch eine milde Behandlung dieser Substanz mit HCl aufgehoben werden. Da Glutamin als solches keinen nachteiligen Einfluss ausübt, wird als Arbeitshypothese angenommen, dass Glutamin in gebundener Form die Ursache der schädlichen Wirkung des Weizens ist. Es scheint, dass Nahrungsmittel, die einen hohen Quotienten von amidhaltigem/amidfreiem Nitrogen haben, schädlich sind, während Nahrungsstoffe mit einem niedrigen Quotienten harmlos sind. In einer Anzahl von Nahrungsmitteln ist dieser Quotient bestimmt worden.

Enfermedad celiaca. V. *Experimentos para determinar los efectos dañinos de la gliadina del trigo.*

El efecto perjudicial de la gliadina (que contiene 43 % de glutamina) en enfermos celiacos puede ser eliminado tratando esta substancia con HCl. Como la glutamina como tal no tiene efectos dañinos se acepta como hipótesis de trabajo que la forma ligada es la causa de dicho efecto en el trigo. Parece que alimentos conteniendo una elevada relación nitrógeno amidado/nitrogeno no amidado son tolerados mientras que los que tienen una baja relación son perjudiciales. Se determinó esta relación en algunos alimentos.

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Plasma Levels of 17-Hydroxycorticosteroids in Erythroblastosis Fetalis

by CARL A. GEMZELL

The adrenal glands of newborns with erythroblastosis are rarely the site of malformation. Enlarged adrenals with extreme vascularity have been reported but just as often adrenals of normal size have been found. The histological picture of the adrenals seldom show any abnormalities.

KLEIN, FORTUNATO & PAPADATOS (1954) have determined the plasma levels of 17-hydroxycorticosteroids in six infants with erythroblastosis, 4 to 30 hours post partum. In comparison with the plasma levels of 14 normal infants 2 to 5 days post partum, the steroid levels of the six patients were elevated.

In this study the plasma levels of 17-hydroxycorticosteroids in the umbilical cord of 79 infants born of Rh-isoimmunized mothers were compared to the plasma levels in the umbilical cord of infants delivered of normal mothers. In the group of infants born of isoimmunized mothers 68 had a positive direct Coomb's test.

Materials and Methods

Peripheral blood was drawn from 79 Rh-isoimmunized mothers immediately post partum. Sixty-four of the mothers had a normal delivery, 10 were delivered after cervical dilatation with metreurynter, and 3 were delivered by Caesarean section. Two had a normal labour but delivered a dead infant. The average age of the Rh-isoimmunized mothers who were all multiparae was 31 years.

Fourty-seven women (27 primiparae and 20 multiparae) were selected at random and used as controls. The average age of these mothers was 27 years.

Blood was drawn from the umbilical cord of the 79 infants delivered of the Rh-isoimmunized mothers. The average weight of the infants was 3,460 g. Exchange transfusion was performed in 36 of the infants, approximately 3 hours post partum, and at the same time a new blood sample was taken from the umbilical cord from the infants. Seventy-seven of the infants left the hospital after an average treatment of 11 days (6–33 days), two were stillborn.

Blood was also drawn from the umbilical cord of 47 infants delivered by normal mothers. The average weight of these infants was 3,500 g.

TABLE 1

Plasma levels of 17-hydroxycorticosteroids in normal and Rh-isoimmunized mothers and in the umbilical cord of their infants.

Groups	Average age	No. of mothers	Plasma levels of 17-hydroxycorticosteroids in μg/100 ml of plasma	
			mothers	infants
Rh-isoimmunized:				
Normal delivery	31	64	35.5±2.23	7.66±0.81
Metreurynter	31	10	29.7±4.84	4.27±0.78
Caesarean section	35	3	33.4	5.10
Stillbirth	33	2	15.7	0
Controls:				
Primiparae	24	27	42.2±3.79	28.0±2.65
Multiparae	29	20	23.4±2.76	15.8±1.97

The concentration of 17-hydroxycorticosteroids in plasma was determined by the method of NELSON & SAMUELS (1952). Plasma samples of approximately 10 ml were extracted 3 times with chloroform. The chromatography was carried out on magnesiumsilicate-Celite columns. The samples were assayed colorimetrically using a Beckman spectrophotometer at 370, 410 and 450 mμ with microcuvettes of 0.5 ml. Correction for background absorption was made by using the colour correction equation described by ALLEN (1950).

The 17-hydroxycorticosteroids are expressed in microgram per 100 ml of plasma. The average plasma level of 17-hydroxycorticosteroids of 22 healthy persons at 8 a.m. is 8.5±1.41 μg. The difference between duplicates is found to be ±12 per cent.

Results

Plasma levels of 17-hydroxycorticosteroids in mothers following labour.—The average plasma level of 64 Rh-isoimmunized mothers immediately after normal deliveries was 35.5 μg per 100 ml of plasma and of 20 multiparae with normal deliveries 23.4 μg. This difference in steroid concentration of venous plasma between Rh-isoimmunized multiparae and normal multiparae is significant. The average steroid concentration of 10 mothers delivered after cervical dilatation with metreurynter was 29.7 μg and of 3 mothers delivered by Caesarean section was 33.4 μg (Table 1 and Fig. 1).

No significant difference was found between the Rh-isoimmunized and the normal multiparae as far as age of the women, time in labour and weight of the infants were concerned.

Plasma levels of 17-hydroxycorticosteroids in the umbilical cord.—The average plasma level of 17-hydroxycorticosteroids in the umbilical cord of

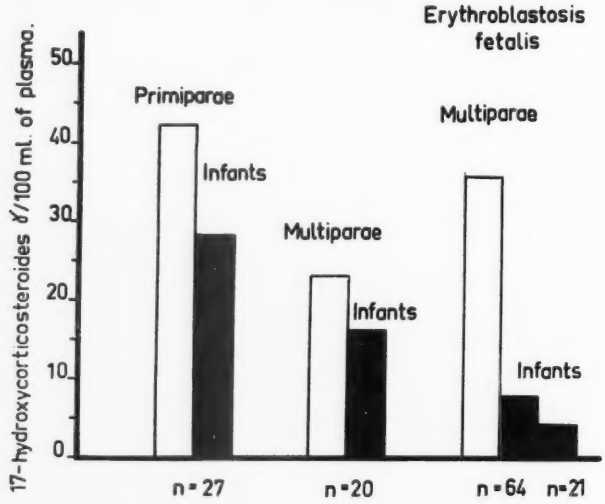

Fig. 1. Plasma levels of 17-hydroxycorticosteroids in normal and Rh-isoimmunized mothers and in the umbilical cord of their infants. Determinations in the infants with erythroblastosis are done at delivery and at exchange transfusion 3 hours later.

infants delivered of 64 Rh-isoimmunized mothers with normal deliveries was 7.7 μg per 100 ml of plasma and in the umbilical cord of infants delivered of normal multiparae 15.8 μg (Table 1 and Fig. 1). The difference in steroid concentration of umbilical cord plasma of the infants born of Rh-isoimmunized mothers and the normal mothers is highly significant ($p < 0.001$). The average plasma level in the umbilical cord of the infants delivered of the Rh-isoimmunized mothers where a metreurynter was used in labour was 4.3 μg and in the umbilical cord of those infants who were delivered by Caesarean section was 5.1 μg (Table 1).

No difference in the steroid concentration of the umbilical cord blood was found between infants delivered after long or short labour, or between newborns weighing more than or less than 3,500 g (Table 2).

The concentration of 17-hydroxycorticosteroids in the umbilical cord did not vary between the infants who were treated with exchange transfusion and the infants who received no blood. Nor was any difference found between those infants who had a hemoglobin under 80 per cent and those who had a hemoglobin over 80 per cent or between those infants with less than 3.0 mill. erythrocytes and those with more than 3.0 mill. (Table 2).

No significant difference was found between the plasma steroids of those infants who were delivered of mothers with a high antibody titre and those infants delivered of mothers with a low titre (Table 2).

TABLE 2

Plasma levels of 17-hydroxycorticosteroids in Rh-isoimmunized mothers and in the umbilical cord of their infants.

Groups	No. of mothers	Plasma levels of 17-hydroxycorticosteroids in µg/100 ml of plasma	
		mothers	infants
Exchange transfusion	36	34.3	8.00 ± 1.05
No exchange transfusion	28	36.5	7.15 ± 1.28
Hemoglobin:			
<80 per cent	30	36.2	8.80 ± 1.15
≥80 per cent	34	34.1	6.50 ± 1.14
Erythrocytes:			
≤3.0 mill.	18	34.7	9.00 ± 1.54
>3.0 mill.	46	35.1	6.51 ± 0.94
Antibody titre:			
<1:32	44	37.5	8.50 ± 1.10
≥1:32	20	30.9	5.80 ± 0.86
Time in labour:			
< 6 hours	32	33.1	7.00 ± 1.41
<12 hours	43	35.8	7.80 ± 0.98
≥12 hours	21	35.3	7.06 ± 1.33
Weight of infant:			
<3,500 g	30	32.9	6.50 ± 0.94
≥3,500 g	34	37.6	8.64 ± 1.26

In 21 infants, treated with exchange transfusion, the average plasma level of steroids in the umbilical cord 3 hours post partum was 3.96 ± 0.72 µg. At delivery the same 21 infants had an average steroid level of 7.64 ± 1.29 µg. Thus a small, though not significant, decrease occurred in the 3 hours period post partum.

Discussion

As has been shown in a previous paper (GEMZELL 1954), the plasma levels of 17-hydroxycorticosteroids following a normal labour are significantly higher in primiparae (42.2) than in multiparae (23.4). The reason for this difference is not clear but it seems most likely to assume that the traumatic experiences and the psychological strain (FRANKSSON & GEMZELL 1955) of the first labour are more severe than during the second and third ones.

In the Rh-isoimmunized mothers who are all multiparae, the plasma level of 17-hydroxycorticosteroids is significantly higher than the steroid level of normal multiparae. It may be due to the disease of the expected infant that the psychological strain is more prominent. Age of the mothers, time in labour and weight of the infants did not differ significantly between the Rh-isoimmunized multiparae and the normal multiparae and thus could not influence the steroid levels.

As has been suggested by GEMZELL (1954) the plasma level of 17-hydroxycorticosteroids in the umbilical cord of infants immediately post partum reflects the traumatic stress of labour. After Caesarean section, for example, the level is very low while in infants delivered by forceps due to signs of fetal distress and hypoxia the level is high. It might be suggested, therefore, that in labour of similar difficulties the steroid level indicates the functional state of the fetal adrenals.

In the umbilical cord of the newborns delivered of the Rh-isoimmunized mothers the plasma levels of 17-hydroxycorticosteroids are lower than the plasma levels of infants born of normal multiparae. Since age of the mothers and traumatic factors, as well as time in labour and weight of the infants, are uniformly distributed in the two groups, erythroblastosis might be responsible for the change. If this is true the more diseased infants may have a lower steroid level than the healthy ones. However, when separating the infants into groups according to exchange transfusion, hemoglobin concentration and number of erythrocytes no such difference could be found. Likewise, no difference was found between the infants delivered of mothers with a high antibody titre and infants delivered of mothers with a low titre. Thus no connection can be shown between the antibody titre of the mothers and the steroid levels in the umbilical cord of their infants and no connection could be established between the steroid level in the umbilical cord and the severity of the erythroblastosis.

This investigation does not confirm the results reported by KLEIN *et al.* (1954). However, the two investigations may be difficult to compare as the blood samples were taken at different time intervals post partum. KLEIN *et al.* determined the corticosteroids in the peripheral venous blood of the infants, 4 to 30 hours post partum. In this study the determinations were done at the time of delivery in the umbilical cord. It is generally considered and has been confirmed in this study that the plasma levels of 17-hydroxycorticosteroids decrease rapidly post partum. If KLEIN *et al.* have found a high level several hours post partum, the level at delivery may be still higher. However, of their 6 patients only two showed an elevated steroid level, the other four had a level that was lower than the level found in this study 3 hours post partum.

The results of this study seem to show that the adrenals of the infants born of Rh-isoimmunized mothers do not respond to labour as do the adrenals of infants delivered of normal mothers. The reason for this inhibition of adrenal function is not clear. It may be due to the hemolytic anemia in erythroblastosis that the adrenals are affected, but no correlation was found between the severity of the disease and the height of the steroid level.

If the adrenal-pituitary system of the infant is functionally altered, it might be suggested that the changes are secondary, since the fetal adrenals in erythroblastosis rarely show pathologic changes. Other factors warrant consideration in determining the nature of these changes, i.e. liver or placental function.

Summary

After a normal labour the plasma levels of 17-hydroxycorticosteroids of 64 Rh-isoimmunized mothers who are all multiparae are significantly higher than the plasma levels of normal multiparae. It is suggested that the Rh-isoimmunized mothers due to the disease of their expected infants are under a more pronounced psychological strain than the normal multiparae.

In the umbilical cord of the infants born of the Rh-isoimmunized mothers with a normal labour the plasma levels of 17-hydroxycorticosteroids are significantly lower than the steroid levels of infants born of normal multiparae. No connection could be shown between the antibody titre of the mothers and the steroid levels of the umbilical cord of their infants and no connection could be established between the steroid level in the umbilical cord and the severity of the erythroblastosis.

Le taux plasmatique des 17-Hydroxycorticostéroïdes au cours de l'érythroblastose foetale.

Le taux plasmatique des 17-Hydroxycorticostéroïdes a été étudié chez 64 mères présentant une isoimmunisation Rh, toutes multipares et après un accouchement normal. Ce taux a toujours été nettement plus élevé que chez des multipares normales. L'hypothèse soulevée est celle de conditions psychologiques défavorables chez les mères Rh immunisées. Le taux des 17-Hydroxycorticostéroïdes dans le sang du cordon des enfants nés de mères Rh immunisées aprés un accouchement normal, est nettement plus bas que celui d'enfants nés de mères multipares normales. On n'a pu établir aucun rapport entre le taux des stéroïdes du sang et le taux d'anticorps du sang de la mère, ni entre le taux des stéroïdes du sang du cordon ombilical et l'importance de l'érythroblastose.

Plasmaspiegel der 17-Hydroxycorticosteroide bei Erythroblastosis fetalis.

Nach einer normalen Geburt waren die Plasmaspiegel der 17-Hydroxycorticosteroide von 64 Rh-isoimmunisierten Müttern, durchwegs multiparae, signifikant höher als die Plasmaspiegel normaler multiparae. Es wird angenommen, dass die Rh-isoimmunisierten Mütter infolge der Krankheit der zu erwartenden Kinder unter einer höheren psychologischen Belastung stehen, als die normalen Mehrgebärenden. Im Nabelschnurblut von Kindern Rh-isoimmunisierter Mütter mit normaler Geburt sind die Spiegel der 17-Hydrooxycorticosteroide signifikant niedriger als die Steroidspiegel

bei Kindern normaler Mehrgebärender. Es konnte keine Beziehung zwischen den Antikörpertitern der Mütter und den Steroidspiegeln im Nabelschnurblut ihrer Kinder und keine Beziehung zwischen den Steroidspiegeln im Nabelschnurblut und der Schwere der Erythroblastose gefunden werden.

Nivel plasmático de 17-Hidroxicorticosteroides en eritroblastosis fetalis.

Después de un parto normal, los niveles plasmáticos de 17-Hidroxicorticosteroides en 64 multíparas Rh isoinmunizadas, fueron significativamente más altos que los de multíparas normales. Se sugiere que las madres isoinmunizadas, debido a la probable enfermedad del futuro hijo, esten psicológicamente más afectadas que las del otro grupo. En el plasma del cordón del primer grupo, los 17 Hidroxicorticoesteroides fueron significativamente mas bajos que el los hijos de madres sanas. No se pudo establecer relación alguna entre el título de anticuerpos de la madre y los esteroides del hijo ni entre el nivel de esteroides y la severidad de la eritroblastosis.

Acknowledgment

The author is greatly indebted to Dr. Birger Broman for many helpful suggestions. The author also wishes to express his gratitude to Mrs. Mona Jäderholm and Miss Ingegerd Almqvist for valuable technical assistance.

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Bone Salt Formation Measured in Infants by Means of P^{32}

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Introduction

Balance studies and studies of the skeletal structure do not give sufficient information concerning the nature of disturbances in the metabolism of bone. The tracer technique has opened new possibilities for investigating the metabolic pathways, and during recent years the metabolism of bone salt has been extensively studied in animals with the aid of radioactive isotopes. Mainly on account of difficulties in the interpretation of isotope data, however, this technique has hitherto not often been employed for metabolic bone studies in humans.

However, in contrast to wide-spread opinion, we have recently demonstrated that in animals the isotope technique permits accurate determinations of the rates of new formation (accretion) and resorption of bone salt. In addition, the exchange reactions between the bone salt crystals and the blood can be studied quantitatively.

The present investigation shows how the isotope technique can be used for determinations *in vivo* of the accretion rate of bone salt in humans.

Principles for Computation

(See BAUER, CARLSSON and LINDQUIST (1955 a) for a detailed analysis of the principles involved).

The amount of an isotope such as P^{32} present in the inorganic portion of a calcified tissue can be written

$$P^{32}_{obs} = P^{32}_{E} + P^{32}_{A} - P^{32}_{R} \qquad (1)$$

P^{32}_{obs} = total amount of P^{32} present in the inorganic portion of a calcified tissue.
P^{32}_{E} = amount of P^{32} present in the exchangeable fraction of the bone salt.
P^{32}_{A} = amount of P^{32} incorporated into the non-exchangeable fraction of the bone salt through accretion.

[1] Technical assistance: T. MAGNUSSON, M. LINDQVIST and B. JÖNSSON.

P_R^{32} = amount of P^{32} removed from the inorganic portion of the bone through resorption.

As the magnitude of P_E^{32} is directly proportional to the rapidly declining specific activity $\left(\frac{P^{32}}{P^{31} + P^{32}}\right)$ of the inorganic serum P, the magnitude of P_E^{32} will after a sufficiently long interval approach zero. If this interval is so short that the bone salt laid down during this interval has not been reached by the resorption process, P_R^{32} may also be disregarded.

Thus, $P_E^{32} = 0$, and $P_R^{32} = 0$, equation (1) may then be written

$$P_{obs}^{32} = P_A^{32} \tag{2}$$

However,

$$P_A^{32} = A \times T \times S_M \tag{3}$$

where

A = rate of P accretion.
T = interval of time between administration of a single dose of P^{32} and observation.
S_M = *average* specific activity of serum P during this time interval.

Combining (2) and (3) we obtain $$A = \frac{P_{obs}^{32}}{T \times S_M} \tag{4}$$

Actually, this equation has proved valid in computations of the accretion rate of bone salt in rats when Ca^{45}, P^{32}, or Na^{22} are employed as tracers.

In the present investigation, following intramuscular injection of P^{32} to children, determinations of the specific activity of the serum and urine inorganic P and of bone biopsy specimens have given sufficient data for the computation (according to eq. (4)) of the rate of bone salt accretion in the upper part of the tibia shafts.

Experimental

The experimental series comprised four children; see *Case Reports* below.

Administration of P^{32}. $H_3P^{32}O_4$ of a high specific activity (obtained from Harwell) and Na_2HPO_4 were added to a physiological saline solution until the P content of the solution was about 7 mg per 100 ml. Each child received an intramuscular injection in the gluteal region of 1–2 ml of this solution, the dose being in each case 2 μC/kg body weight.[1] (Concerning safeguards in the use of P^{32} in humans, see Ström.) The children were fasting up to one hour after the P^{32} injection which always was performed at 8.00 a.m. During the experimental period the main food constituent was so-called citric acid milk, i.e. milk containing 0.4 per cent citric acid.

Collection of samples. By finger puncture, capillary *blood* was taken at the following intervals after the P^{32} administration: $^1/_4$, $^1/_2$, 2, 3, 4, 8, 12, and 24 hours. Immediately after each puncture, 0.5 ml serum was mixed with 2.5 ml of 10 % trichloroacetic acid and centrifuged. The supernatant was examined for radioactivity and inorganic phosphorus.

[1] We are indebted to K. Lidén, Ph.D., for measurement of the doses.

Fig. 1. X-ray of the right tibia of Case III with site of puncture indicated.

Twenty-four-hour specimens of *urine* were collected in special bottles for 16 to 18 days following the administration of P^{32}. Only in two cases was it possible to collect the urine quantitatively. The urine was examined for radioactivity and inorganic phosphorus.

Two *bone* specimens were taken from each child, the first specimen from the left tibia and the second specimen from the right tibia about 7 and 16 days respectively after the administration of P^{32}. The bone specimens were taken with a borer, which had an inner diameter of 3 mm. The specimens were taken in the upper part of the tibia at the junction of the proximal $^1/_4$ and the next proximal $^1/_4$ of the tibia, where the antero-medial bone surface lies immediately beneath the subcutis. In order to get the two specimens from corresponding parts of the tibias the sites of puncture were indicated by X-ray (see Fig. 1). By this technique a cylindrical piece of mainly compact bone was generally obtained. With one exception—the 8-day specimen of Case III—all adherent spongy bone was removed. On one occasion—the 16-day specimen of Case IV—the indicator plate had not stayed in place, with the result that the puncture in this case was carried out too near the crista anterior of the tibia. The specimens were carefully dissected free from adhering soft tissue and were then shaken several times

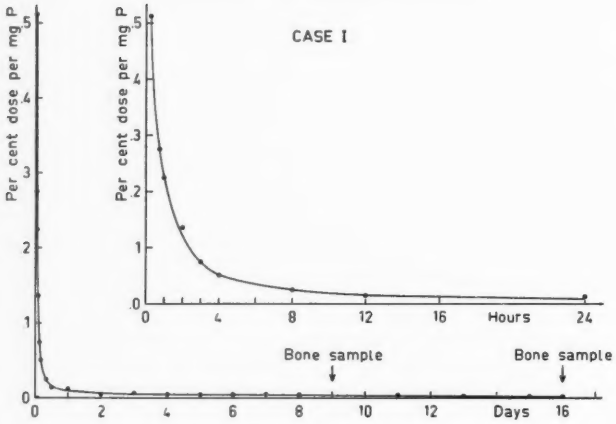

Fig. 2.

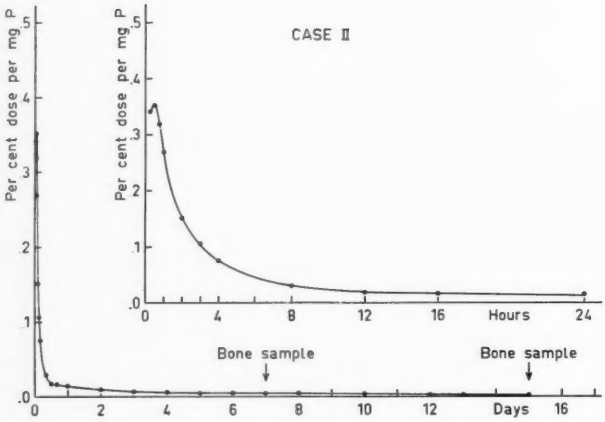

Fig. 3.

Fig. 2–5. Specific activity of serum and urine inorganic P following intramuscular injection of P^{32} to the children of the experimental series.

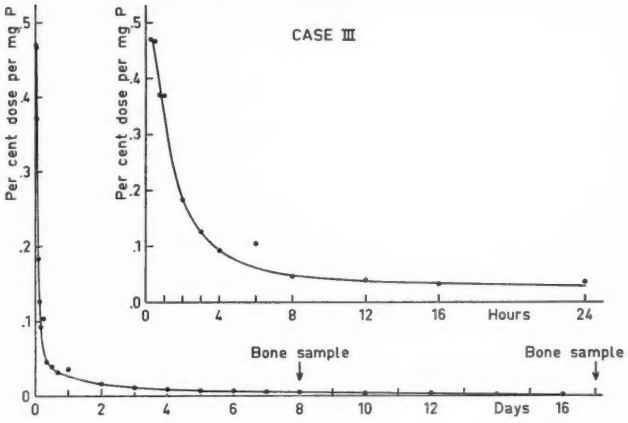
CASE III
Per cent dose per mg P
Hours
Bone sample
Bone sample
Days

Fig. 4.

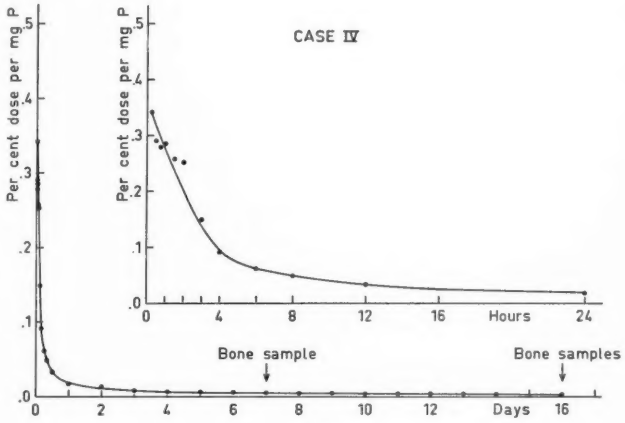
CASE IV
Per cent dose per mg P
Hours
Bone sample
Bone samples
Days

Fig. 5.

with physiological saline solution, in order to remove as much as possible of blood and bone marrow. The specimens were ashed in an electrically heated muffle for 2 hours, were weighed (accuracy ± 0.1 mg), and examined for radioactivity and content of Ca and P.

Determinations of radioactivity were made on liquid samples. The technique used was that of CARLSSON. By comparison with the activity of a standard solution containing the dose of P^{32} in a certain volume, the activity of the samples could be expressed as per cent of dose administered.

Determinations of the P^{32} content of the serum were carried out on the trichloroacetic acid supernatant. The amount of organic phosphorus in the urine being negligible, the determinations of activity were made directly on the urine, acidified to pH 4 to 5 by means of glacial acetic acid. The bone ash was dissolved in 1 ml 1 *N* HCl, and the activity determinations were made on these liquid samples.

Determinations of phosphate in blood and urine. The inorganic P of the serum was determined by the method of YOUNGBURG and YOUNGBURG, and in the urine by the method of FISKE and SUBBAROW (see WARLEY).

Determinations of calcium and phosphorus in the bone specimens were made on the HCl solution of the bone ash. The methods used were those of CLARK and COLLIP and YOUNGBURG and YOUNGBURG respectively.

Case Reports

Case I (*Normal child*).—Boy; 6 months of age; weight 9,100 g; birth weight 4,000 g; sixth child of healthy parents. After birth the child was breast-fed for 2 weeks and then received a diet of citric acid milk supplemented by vitamins A and D in prophylactic doses. He was admitted to the clinic for pertussis, from which he recovered after 3 weeks at the clinic. When examined before the experiment the patient was found to be healthy and to have gained normally in weight. Skeletal X-ray did not reveal any rachitic signs. (Fig. 2.)

Case II (*Normal child*).—Boy; 15 months of age; weight 10,300 g; birth weight 2,700 g; fourth child of healthy parents. After birth the child was breast-fed for 8 months and then received a diet containing cows milk and ordinary dietary supplements including vitamins A and D in prophylactic doses. He was admitted to the clinic for a burn injury. His general condition was good during the stay at the clinic. When examined before the experiment the patient was found to be healthy and to have gained normally in weight. Skeletal X-ray did not reveal any rachitic signs. (Fig. 3.)

Case III (*Mongolism*).— Boy; 5 months of age; weight 6,100 g; birth weight 2, 800 g; second child of healthy parents. After delivery, which was rapid, his general condition was extremely bad, and he had repeated cyanotic attacks. He was therefore transferred from the maternity hospital to the pediatric clinic, where after 3 months his condition had improved. He had gained in weight and was in a rather good condition. He was readmitted to the clinic because of a slight upper respiratory infection from which he recovered within a week and again gained normally in weight. He had typical mongolian features. In the clinic as well as at home he had received citric acid milk. Vitamins A and D were given in prophylactic doses from about 6 weeks of age. Skeletal X-ray did not reveal any rachitic signs. (Fig. 4.)

Case IV (*Mongolism*).—Boy; 12 months of age; weight 8,600 g; birth weight 3,000 g; sixth child of healthy parents. After birth he received breast milk and later on citric acid milk with ordinary dietary supplements. Vitamins A and D were given in

prophylactic doses, but not regularly. He was admitted to the clinic for a bronchopneumonia, from which he soon recovered. He had typical mongolian features. At the time of experiment he was free from symptoms of infection, his general condition was good, and he had gained in weight. Skeletal X-ray (O. OLSSON, M.D., Lund) showed a slight general decrease in density but no definite metaphyseal signs of rickets. (Fig. 5.)

Results

In Fig. 2–5 the specific activity of the serum P during the initial 24- to 48-hour period and that of the urinary P during the whole experimental period are plotted for each case. From these curves the average specific activities (S_M) during the various intervals have been computed for each case (Table 1). In those cases (III and IV) in which the urine could be collected quantitatively, the specific activity of the P of the initial 24-hour urine specimen was approximately the same as the average specific activity of the serum P during the initial 24-hour period. In Case III these values were 0.062 and 0.067 respectively, and in Case IV, 0.067 and 0.066 respectively, the values expressed in per cent of dose per mg P. (Thus, if the urine can be collected quantitatively, the determination of the specific activity can be confined to the urine.)

In Table 1 are given the data which form the basis of the calculation of the accretion rate according to eq. (4) (page 478). In the normal cases (I and II) the values of the two bone specimens taken at different intervals after the administration of P^{32} were in good agreement, the values for Case I being 0.017 and 0.015, respectively, and for Case II, 0.0116 and 0.0103, respectively, expressed as mg P per day per mg P of sample. These results indicate that eq. (4) was valid.

The accretion rate in the spongy bone was higher than in the compact bone, as seen in Case I where 16-day values of 0.029 and 0.015, respectively, were obtained. Consequently, if adherent spongy bone is not removed, a misleading value may be obtained. This is shown also by the 8-day specimen of Case III.

In Case IV there was a relatively great difference between the values of the accretion rate at the two intervals, the values for the 7-day and the 16-day specimens being 0.0047 and 0.0067, respectively. This is probably due to the fact that the two specimens were not taken from corresponding parts of the tibias (cf. page 479).

The high Ca/P ratios given in Table 1 indicate that there was but a slight contamination with organic P in the bone samples. The spongy bone specimen of Case I forms a possible exception in this respect. There is of course a relatively greater amount of organic P adherent to the spongy than to the compact bone.

TABLE 1

Data forming basis for calculations[1] of the accretion rate of bone salt in specimens[2] from tibias of children.

Subject	Interval after administration of P^{32} (T) (days)	Average specific activity (S_M) of serum (urine) P (% of dose per mg P)	Bone specimen					Accretion rate (A) (mg P per day per mg P of bone specimen)
			Ash weight (mg)	Ca (mg)	P (mg)	Ca/P	Activity (P^{32}_{obs}) (% of dose)	
Case I (Normal child)	9	.0093	6.0	2.24	.96	2.33	.00141	.017
	16	.0061	6.4	2.59	1.12	2.31	.00158	.015
	16	.0061	1.8	.66	.33	2.00	.00091	.029[3]
Case II (Normal child)	7	.0133	4.7	1.78	.75	2.38	.00080	.0116
	15	.0075	7.5	2.95	1.30	2.28	.00151	.0103
Case III (Mongolism)	8	.0189	4.5	1.66	.80	2.28	.00415	.038[4]
	17	.0102	4.0	1.38	.61	2.25	.00209	.020
Case IV (Mongolism)	7	.0168	6.0	2.38	1.06	2.25	.00058	.0047
	16	.0095	18.7	7.53	3.55	2.12	.00362	.0067

[1] Eq. (4), page 478, has been used for the calculations. Note however that the accretion rate (A) has been expressed in terms of mg P per day *per mg P of bone specimen.*

[2] The specimens consisted of compact bone except one of the 16-day specimens of Case I and the 8-day specimen of Case III.

[3] The specimen consisted of spongy bone.

[4] The specimen consisted of both compact and spongy bone.

Discussion

In the proximal part of the tibia shafts of normal infants the values for the accretion rate were 0.016 (Case I) and 0.011 (Case II), respectively, expressed as mg P per day per mg P of sample, corresponding to about 0.05 per cent *per hour* (Table 2).

The percentage net increase in inorganic phosphorus in the skeleton must be the same as the percentage net increase in calcium of the whole body, owing to the fact that practically all calcium of the body (more than 99 per cent) is contained in the skeleton and that the bone salt Ca/P ratio is practically constant. If on the average a child contains 20 g of calcium at birth and gains about 0.2 g calcium a day (see SHERMAN), the net increase in calcium at 12 months of age may be calculated to be about 0.01 per cent per hour. Thus the net increase constitutes one fifth of the accretion rate. This

TABLE 2

Accretion rate of bone salt as compared to laboratory findings.

Subject	Age (months)	Body weight (g)	Serum Ca (mg per 100 ml)	Serum P (mg per 100 ml)	Ca × P	Alk. phosphatase (Bodansky units)	Accretion[1] rate (mg P per day per mg P of bone specimen)
Case I (Normal child)	6	9,100	9.8	5.7	55.9	18	.016
Case II (Normal child)	15	10,300	9.4	6.6	62.0	14	.011
Case III (Mongolism)	5	6,100	9.8	5.5	53.9	20	.020
Case IV (Mongolism)	12	8,600	10.1	4.1	41.4	9	.0057

[1] The mean value for each case of the accretion rates of the compact bone specimens registered in Table 1.

proportion of net increase to accretion in the proximal part of the tibia shafts in normal infants is of the same order as that observed in the tibia of young rats (BAUER, CARLSSON and LINDQUIST 1955 a).

In accordance with the fact that the percentage increase in body weight drops with age, it is seen from Table 2 that the highest accretion value of Cases I–III is that of the child with the lowest age (and weight), and *vice versa*.

In Case IV the accretion rate was lower than in the other cases, viz. 0.0057 mg P per day per mg P of sample (Table 2). This may possibly be related to the low value of inorganic P in the serum (4.1 mg per 100 ml). This may in turn be due to a certain degree of vitamin D deficiency; in contrast to the other children of the series, this child had not received a regular prophylactic dose of vitamin D, nor was the skeletal bone structure quite normal (as judged from the X-ray investigation). The accretion rate in rickets will be studied in a forthcoming paper (BAUER, CARLSSON and LINDQUIST 1955 b).

Summary

A technique has been developed for evaluation of the rate of new formation (accretion) of bone salt in infants by means of P^{32}. In the proximal part of the tibia shafts

of normal infants the percentage of bone salt added through accretion was estimated to about 0.05 per cent per hour, i.e. about five times the net increase.

Mesure de la formation des sels dans les os de nourrissons au moyen du P^{32}.

L'auteur a mis au point une technique pour évaluer par le P^{32} le degré de formation nouvelle (accroissement) de sel dans les os. On a évalué que le pourcentage de sels osseux ajouté par accroissement dans la partie proximale de la diaphyse du tibia chez des nourrissons normaux est d'environ 0,05 pour cent par heure, ce qui représente environ cinq fois l'augmentation nette.

Bestimmung der Knochensalzbildung bei Säuglingen mit Hilfe von P^{32}.

Um die Neubildung von Knochensalzen bei Säuglingen zu bestimmen, ist mit Hilfe von P^{32} eine neue Technik entwickelt worden. Im proximalen Teil des Tibiaschaftes normaler Säuglinge wurde der Prozentsatz der durch Anlagerung hinzugekommenen Knochensalze auf ungefähr 0.05 % pro Stunde geschätzt, d. h. etwa fünfmal soviel wie die Nettozunahme.

Formacion de sales oseas en el niño medidas por medio del P^{32}

Por medio del P^{32} se midió la tasa de neoformación (acresión) de sales óseas en niños. En la parte proximal de la diáfisis tibial de niños normales, la acresión salina fué estimada en alrededor del 0,05 % pro hora, es decir alrededor de 5 veces el aumento neto.

Acknowledgement

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Kwashiorkor and Malnutrition

by H. C. TROWELL, J. N. P. DAVIES and R. F. A. DEAN

The paper by GÓMEZ, GALVÁN, CRAVIOTO and FRENK (3) with the title *Malnutrition and Kwashiorkor* raises some interesting matters for discussion. We have quoted from many of the excellent publications of the Mexican group in a recent monograph (7) but some amplification may be of value.

1. GÓMEZ *et al.* compare what they call "Third degree Malnutrition" with kwashiorkor, and show, as they have done previously (4), that they are very similar. We agree, and have in fact devoted considerable efforts to trying to show that diseases called by many other names, such as *Mehlnährschaden*, *Sindrome policarencial infantil*, *Distrofia pluricarencial hidropigenica*, *Distrofia da farine*, are also similar.

2. GÓMEZ *et al.*, when they are writing in English, prefer the term "malnutrition" to a number of terms which are more or less synonymous. They say (p. 339): "If, independently of their etiology, the various forms of nutrient disturbances are only stages of a single disease with a single pathogenesis, it is only logical that a single name be used, viz. Malnutrition; and it is practical to class the different stages by degrees."

3. This argument depends on proving that *all* malnutrition is of the same type. We do not think that is possible. There are many forms of malnutrition, of which kwashiorkor is one. To us kwashiorkor (or a similar disease called by any other name) represents the end-result of a process of malnutrition that is different from the end-result of other processes of malnutrition or undernutrition. Among the authorities that GÓMEZ *et al.* call to their aid are CZERNY and KELLER (2) and MARRIOTT (6), but the German workers sought to make a clear distinction between *Mehlnährschaden* and the other conditions of malnutrition and undernutrition that they described: and it is possible to believe that Marriott today would not be pleased to read that he had implied that "the biochemical lesions are always the same, whether serious diarrhea is present or not, and whatever the etiology of the picture" (GÓMEZ *et al.*, p. 339). On p. 463 of his remarkable paper MARRIOTT described dramatically the picture of acute dehydration seen in the "acute toxic-like condition usually following severe diarrhea": the description in-

cluded air hunger, a raised rectal temperature, very scanty urine, and concentration of the blood, with an increase in the blood protein "as great as 50 per cent above the normal for the age". On p. 476 he described the more chronic condition of malnutrition in which the infant ultimately "wastes to a skin covered skeleton", "the blood is thin, pale", and "the urine is essentially normal in amount"—a condition for which he preferred the term "athrepsia" and in which he found "that the concentration of protein in the serum of these infants was usually lower than the average for normal infants of the same age". He recognised that the "toxic-like condition" might follow the "athrepsia", but he was in fact trying to define two different pathological states—"two types of nutritional disturbances"—neither of which resembles closely kwashiorkor as we see it in Uganda. We think that he would not have said (p. 462) "In the great majority of instances the pathological findings on infants dead of nutritional disturbances are essentially negative" if he had performed an autopsy on a Mexican case of "Third degree Malnutrition".

4. Advanced pellagra, scurvy, or hunger edema are "nutrient disturbances" that do not have "a single pathogenesis", do not produce a clinical, biochemical or histological condition like that of kwashiorkor, and do not respond to a high-protein diet in the same way as kwashiorkor. The English word "malnutrition" might be applied to all of them, but to do so would surely be a retrograde step.

5. We, in Kampala, like VÉGHELYI (8) in Budapest, see children suffering from "simple inanition with all the classical signs of infantile atrophy", who differ during life and at autopsy from children who have advanced kwashiorkor, and who resemble Marriott's descriptions. Some of the differences between children with simple inanition, that is to say advanced undernutrition on well-balanced diets, and kwashiorkor (due to an imbalanced diet, low in protein) are shown in Table 1.

6. The use of stages to describe diseases is usually unsatisfactory unless there are clear-cut methods of distinction. Thus, while it may be satisfactory in describing the evolution of a disease such as carcinoma of the uterine cervix, it is not likely to be satisfactory in nutritional diseases in which there are not obvious stages. One of the most important of the features used by GÓMEZ *et al.* for the classification of their cases is the amount that the children are under a standard weight for age, but this method does not seem to us to be entirely satisfactory: malnourished children, when they are seen in hospital, may have much edema or none and the presence of edema, although it must affect the weight, is not a reliable criterion of severity of disease. We are seeking other criteria that will enable us to define our cases objectively.

TABLE 1

Some differences between simple inanition in children and kwashiorkor in children.

	Simple Inanition	Kwashiorkor
Dietary history	Insufficient food	Food having a low protein/calorie ratio: usually the protein/carbohydrate ratio is very low
Hunger	Well preserved until terminal stages	Usually replaced by severe anorexia
Changes of skin and hair	Not usual, even in advanced cases	Usual in advanced cases
Edema	Very unusual	Very often present
Serum albumen	No reduction until terminal stages	Severe reduction
State of subcutaneous fat	Much depleted early in the disease	Considerable amounts retained, until terminal stages
Gross changes in liver and pancreas	Liver not usually fatty: pancreas sometimes atrophic, but easily autolysed	Liver nearly always very fatty: pancreas much reduced in size and not easily autolysed
Activity of pancreatic enzymes	Seldom severely reduced	Always severely reduced
Most effective treatment	Increase in caloric value of diet with normal protein/fat/carbohydrate ratio	Increase in protein of diet, without fat, and with bland carbohydrate
"Nutritional recovery syndrome"	Not described as an effect of treatment	Described as an effect of treatment of Mexican (5) and Central American (1) cases

Summary

The term malnutrition, as it is used in English, is not sufficiently specific, in our opinion, to be used for the disease we prefer to call "kwashiorkor".

Kwashiorkor et « malnutrition ».

Il semble aux auteurs que le terme de « malnutrition », utilisé dans la langue anglaise, ne soit pas suffisamment spécifique de la maladie, et ils préfèrent utiliser celui de Kwashiorkor.

Kwashiorkor und Fehlernährung.

Der Ausdruck Fehlernährung, wie er im englischen Sprachbereich gebraucht wird, ist nicht hinreichend spezifisch, um — nach der Meinung des Autors — für die besser „Kwashiorkor" zu nennende Krankheit gebraucht zu werden.

Kwashiorkor y malnutrición.

El término "malnutrition" tal cual se usa en inglés, no es suficientemente específico, en la opinión de los autores, para aplicarlo a la enfermedad que ellos prefieren llamar Kwashiorkor.

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CASE REPORT

Primary Vitamin-Resistant Rickets[1]

by EILIF GREGERSEN

From the Pediatric Department of the Copenhagen County Hospital at Gentofte (Head: Senior Physician P. W. Bræstrup, M.D.)

According to American reports published in recent years, the incidence of vitamin-resistant rickets is far greater than has previously been assumed. While FREEMANN and DUNSKY only report some thirty cases in the literature up to 1950, HERBERT PEDERSEN and MCCARROL in 1951 mention twenty-five children from an orthopedic pediatric hospital at St. Louis suffering from vitamin-resistant rickets. Since then or simultaneously individual cases have been reported, among other countries from Norway (IMERSLUND), from Sweden (WALLGREN as also WINBERG *et al.*), from England (COLEMAN & FOOTE) and from South Africa (DE WET).

In this country BAAGOE in 1924 mentioned late rickets as a famial anomaly, and FLAMAND CHRISTENSEN in 1940 related a somewhat atypical vitamin-resistant rickets in a brother and sister and their mother.

HERBERT PEDERSEN and MCCARROLL's material prove that the increasing incidence of the illness is hardly real, but is due to better diagnosis. The twenty-five cases reported by them, which had been consistently treated for rickets while in their infancy, had owing to recurring deformities of the lower extremities, mostly diagnosed as chondrodystrophy, been subjected to 122 osteotomies in total, before the diagnosis active rickets was established. The deceptive diagnosis is among other reasons due to the fact that the disease is a familial anomaly—occurring primarily in sisters and brothers and in parents—in sixteen out of the twenty-five cases.

Since the disease and its treatment have assumed increased interest in recent years, I think there is sufficient justification for reporting the following case from the Pediatric Department of the County Hospital at Gentofte.

Case History

Record No. 1217/54. An eight-year-old girl with normal development until she was about twelve months old. At this juncture her motoric development was arrested. Her legs could not support her, her appetite was poor, and her growth was retarded. Upon her first admission to this hospital (April 1948), when twenty-two months old, vitamin-resistant rickets was found with typical clinical, roentgenographic and biochemic manifestations.

Anamnesis with regard to food and family held out no features of interest. Thus the patient had from the time she was six to seven months old received up to 3,500 units of vitamin D daily. She had been born as second child out of three children by healthy parents of normal stature, and there was no tendency to any kind of diseases among the rest of the members of the family.

[1] An abstract of this paper was read before the Danish Pediatric Society, June 2, 1954.

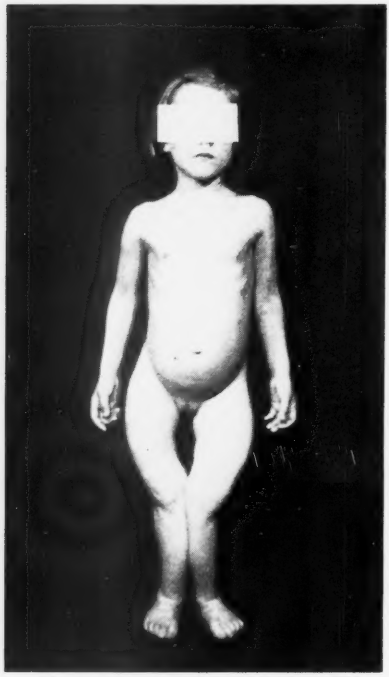

Fig. 1.

After having been hospitalized for six months, the rickets was nearly healed after treatment with 300,000 units of vitamin D daily, and the patient, who at her admission to the hospital was hardly able to sit up, was now capable of walking without support, even if her gait was straddling and marked by lordosis, with the femura and the crura slightly curved.

After her discharge from hospital the patient received 50,000 units of vitamin D daily, and during the first twelve months she was controlled as an outpatient as well as by re-admission to the hospital, and the rickets remained inactive on this dosis. Unfortunately the department at this time lost contact with the patient, and not till five years later (January 1954), at the age of eight, was she re-admitted to the hospital owing to pronounced deformites of the lower extremities and obstructed gait. During the years the department had been out of contact with the patient she received only some 400 units of vitamin D daily each winter. On account of the pronounced deformities of the lower extremities and a fracture of the femur caused by a slight injury, she had twice been admitted to hospitals elsewhere during this period of time.

Physical findings

Fig. 1 shows the typical rachitic deformities with curved femora and bow-legs as also coxa vara with displacement of the trochanters and lordosis. She is flat-footed with her feet in everted position and she walks with a waddling straddling gait.

Fig. 2.

Besides there is enlargement of the epiphyses of the joints of hand and foot as also on the costae, but apart from the rachitic rosary there are no rachitic deformities of the thorax.

The skull reveals moderate frontal "bossing". The anteroposterior diameter is comparatively long, which, as will be commented upon later in this paper, is characteristic of this type of rickets.

The replacement of teeth is somewhat irregular, but on the whole it takes place in due time and there are no special defects in enamel.

Otherwise the physical examination presents no abnormal features, apart from a moderate dwarfish stature (19 cm below normal height).

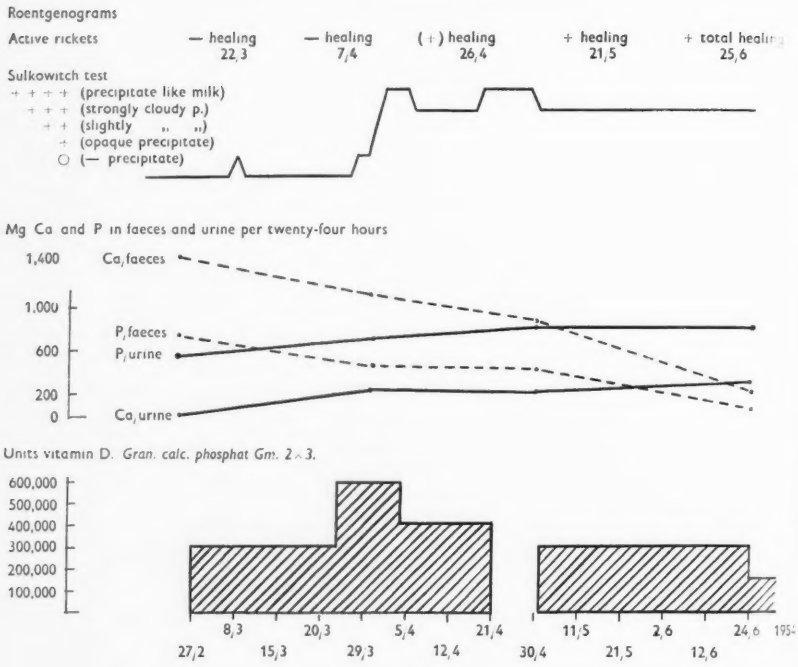

Fig. 3 A.

The *roentgenographic findings* showed changes in the general architecture of the bones, which are coarse and flecked with marked universal halisteresis. The metaphyses and the epiphyseal lines are swollen and widely spaced, with "wooly" frayed contours, and there are pronounced deformities with traces of infractions. *Biopsy* of bones from the distal metaphysis of the femur reveals normally structured bone showing signs of osteomalacia in healing.

Laboratory studies with regard to the calcium-phosphorus metabolism reveals moderately increased alkaline and acid phosphatases as also greatly decreased serum phosphorus but normal serum calcium. The secretion of calcium and phosphorus in the urine is heavily reduced.

All further studies revealed normal conditions, and it is especially emphasized that renal and liver functions were not affected, and that the carbohydrate metabolism, the fat digestion, the electrolytic conditions and the acid-base equilibrium displayed nothing abnormal.

Treatment and course of disease

Dosage of vitamin D appears from Fig. 3A, which shows that a therapeutic effect is not attained, until a dosis of 600,000 units daily is administered, and that the treatment had to be discontinued for a shorter period of time owing to overdosage. After four months of treatment the rickets as shown on Fig. 4B was practially healed with

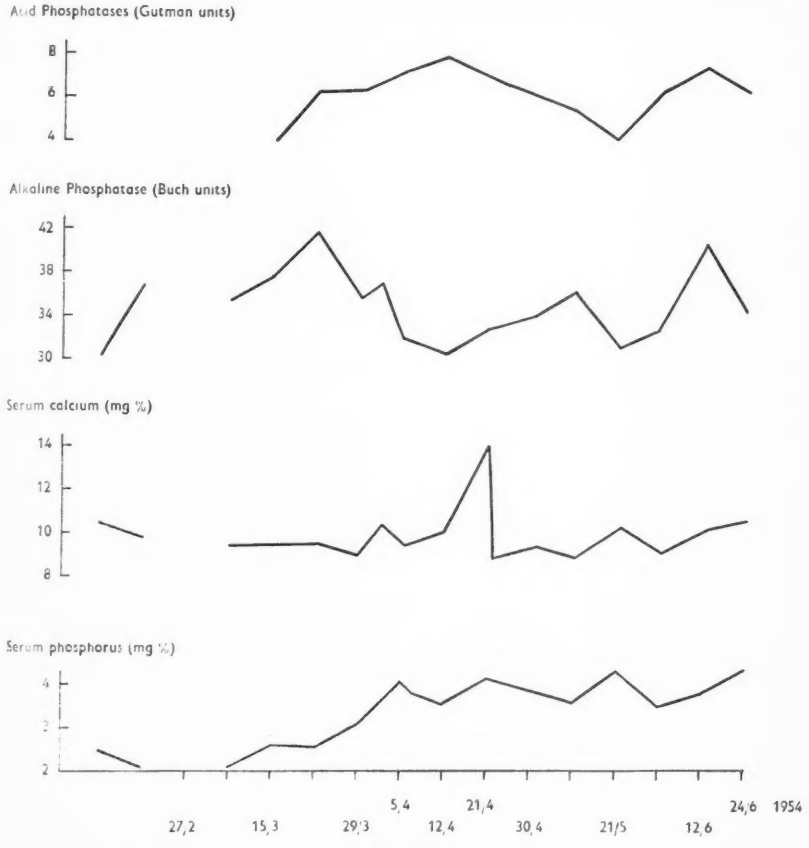

Fig. 3 B.

an absence of enlargement of the epiphyses, a greater density in the configuration of bones, and smoothed-out epiphyseal lines. After this treatment was initiated with a maintenance dosis of 150,000 units vitamin D daily. The preparation used was calciferol.

Blood chemistry: Fig. 3 B shows that serum phosphorus during treatment attained nearly normal levels; it rose from 2.2 to approximately 4 mg %. Alkaline phosphatase has in spite of maximum doses of vitamin D during the whole period of treatment become moderately elevated (about 35 Buch units [normal values in children 5.4–16.1]). During treatment it ought to have declined somewhat, still without attaining normal levels, as long as healing was in progress. The failure of effect in this case on the elevated phosphatase may be due to the fact that the initial level in late rickets or at any rate in this particular case is low, as compared with the phosphatase values in common infantile rickets. The moderately increased values of acid phosphatase are probably due to a secondary parathyroid hyperplasia.

Fig. 4 A.

Fig. 4 B.

The metabolic conditions were drastically improved upon during treatment, as will appear from Fig. 3A and Table 1, which show the results of tests with regard to calcium-phosphorus balances—the tests were undertaken on fixed but otherwise usual food of children, containing 1,157 mg calcium and 1,288 mg phosphorus per twenty-four hours. During the weeks of the second test of balances, her food was supplemented with 698 mg of calcium and 541 mg of phosphorus, administered in the form of granules calcii phosphatis. The values stated, representing the mean values of the single values of four consecutive days and nights, must however be taken with some reservation, the quantities of faeces having varied somewhat from day to day. Fig. 3A and Table I reveal that the excretion of calcium and phosphorus in faeces during twenty-four hours, even during the period with an extra supplement to the patient's food of these substances, declined considerably (maximum decline 1,257 mg of calcium and 696 mg of phosphorus), concurrently with a rise in the urinary excretion of calcium and phosphorus. The percentage excretion of calcium in the urine of the total amount of excretion rose gradually from 0.3 % to maximum 58 %, i.e. the urinary excretion of calcium, which at first was heavily reduced, rose during the intensive treatment first to normal values and the exceeded such values. The same applies to the excretion of phosphorus in the urine which rose from 42 % to maximum 90 % of the total amount of excretion.

TABLE 1

Test of Balances	No. 1 $^{24}/_{2}$–$^{27}/_{2}$		No. 2 $^{26}/_{3}$–$^{29}/_{3}$		No. 3 $^{1}/_{5}$–$^{4}/_{5}$		No. 4 $^{22}/_{6}$–$^{25}/_{6}$	
	Ca	P	Ca	P	Ca	P	Ca	P
Intake per twenty-four hours (mg) . .	1157	1288	1855	1829	1157	1288	1157	1288
Twenty four hours urinary excretion (mg)	4	575	255	712	246	828	304	823
Twenty-four hours excretion in faeces (mg)	1477	783	1150	481	891	433	220	87
Total excretion per twenty-four hours (mg)	1481	1358	1405	1193	1137	1261	524	910
Balance (mg) . . .	− 324	− 70	+ 450	+ 636	+ 20	+ 27	+ 633	+ 378
Percentage urinary excretion of the total amount of excretion[1]	0.3 %	42 %	18 %	60 %	22 %	66 %	58 %	90 %
Administration of vitamin D	Treatment not instituted		600,000 units daily		Vitamin D withdrawn for a short period		300,000 units daily	

[1] Normal values: Calcium: 10–40 % (SUNDERMAN & BOERNER).
Phosphorus: 58–75 % (ELIOT & PARK).

The result of these metabolic changes was that the calcium-phosphorus balance rose from a deficit of 324 mg of calcium and 70 mg of phosphorus to a peak surplus of 633 mg and 636 mg respectively—i.e., there was a maximal retention of 55 % of the amount of calcium supplied. During treatment up to 60 to 80 per cent of the amount of calcium supplied is capable of being retained.

The third test of balances undertaken a few days after discontinuation of vitamin D, showed a surplus of only 20–30 mg of calcium and phosphorus. It is characteristic of vitamin-resistant rickets that the vitamin D effect, as apparently seems to apply in this case, ceases almost immediately after vitamin D having been discontinued.

An initial calcium deficit so pronounced as in this case is only rarely seen, and only as a transient feature in vitamin-resistant rickets.

Discussion

The continual administration of large doses of vitamin D was not established until 19[illegible] when ALBRIGHT published his case, in which he had to employ up to 1.5 mill. un[illegible] daily in order to achieve healing.

Dosage must be fixed under constant control and is governed by the serologic and me[illegible]olic conditions, as well as by the roentgenographic findings, the margin between the [illegible]fficient therapeutic dosis and toxicity being narrow. Above all the serum calcium and [illegible] excretion of calcium in the urine must be watched with regard to the occurrence

of pathologic elements in the urine, polyuria or oliguria and concretions in the kidneys. The weight of the patients must be closely followed, anorexia being one of the incipient signs of overdosage.

The Sulkowitch test,[1] which makes possible rather a rough evaluation of the excretion of calcium in the urine, is one of the easiest and most effective means of controlling the treatment, and it can be performed at home. In case of failing precipitation the rickets will usually be active and require increased doses of vitamin D, but doses must only be increased at intervals of three weeks.

Side effects of a more serious nature are rare in well controlled cases. PEDERSEN and MCCARROL encountered, in one case out of four or three, nausea, vomiting and loss of weight, but in only one case out of twenty-five, hematuria and oliguria, which vanished after a few days' discontinuation of vitamin D and ample supply of fluids, without leaving any evidence of damage to the kidneys.

In our case after scarcely two months of treatment, signs of overdosage appeared, evidence by strong dislike of food and a precipitate like milk by Sulkowitch's test and by a serum calcium of 14.2 mg %. Already the day following the discontinuation of vitamin D, the serum calcium was found to be normal and in the course of a week the symptoms of overdosage had completely vanished.

The duration of treatment is of decisive importance for the final results. When through the disappearance of the serologic, metabolic and epiphyseal disorders, the rickets has become inactive, treatment ought to be continued by means of a maintenance dosis, which is often below one half of the initial, therapeutic dosis. Thus the disease must be kept under constant control, and treatment has to be continued all through childhood and adolescense.

In our case, the disease cannot, strictly speaking, be said to be completely inactive at this juncture, the alkaline phosphatase being not yet within normal limits. However, STEARNS and WARWEG claim complete healing in their case even if the alkaline phosphatase a year later was still double the normal values.

The roentgenographic evidence of an increased content of calcium in the bones and of the disappearance of enlargement of the epiphyses will presumably afford a more reliable proof of inactivity of the rickets than the serologic values.

The object of the treatment is to prevent progression and aggravation of the deformities already existing. These deformities, like the coarse irregular architecture of the bones, must be considered permanent if the age of three or four is exceeded. Thus only the calcium content of the bones and the epiphyseal changes are responsive to vitamin D.

It is still an undecided question whether dwarfism, which is due to functional disturbances in the epiphyses, can be prevented by intensive therapy during a lengthy period of time. Our patient has grown from 103 to 105 cm during the last five-month stay in hospital.

Orthopedic treatment consisting of osteotomies for correction will often prove necessary in many cases at a time when the rickets is in its inactive phase. According to GREEN, side effects are frequent following osteotomies because of increased serum calcium and increased excretion of calcium in the urine, perhaps caused by postoperative immobilisation. Accordingly it is advised to discontinue the administration of vitamin D previous to operation and not to continue with the maintenance dosis until two weeks after the operation.

[1] The reaction has been made on twenty-four hours' urine with reagent and urine in equal proportions.

As formerly mentioned, the skull, in case of vitamin-resistant rickets is often characterized by a prolonged antero-posterior diameter and a decreased transverse diameter. In Imerslund's case the scaphocephaly was so pronounced that decompressive craniotomy became necessary. This deformity of the skull, according to IMERSLUND and COLEMAN & FOOTE is due to a coincident ocurrence of a premature ossification of the sagittal suture.

The etiology of primary vitamin-resistant rickets is still undefined and many theories are put forward, some enzymatic or hormonal defect probably being the cause of the disease.

Summary

A typical case of an eight-year-old girl with primary vitamin-resistant rickets is reported. During treatment with large doses of vitamin D the calcium-phosphorus balance turned positive and the rickets gradually healed. Since the disease has assumed renewed interest in recent years, the problems of therapy are discussed, emphasis being placed on the value of long continued and intensive treatment under constant control.

Rachitisme primaire résistant à la vitamine D.

L'auteur rapporte un cas typique de rachitisme primaire résistant à la vitamine D chez une fillette âgée de huit ans. Durant le traitement avec de fortes doses de vitamine D la balance du calcium et des phosphates devenait positive et le rachitisme guérissait progressivement. La maladie ayant connu un grand intérêt pendant longtemps, l'auteur discute le problème du diagnostic différentiel et du traitement et insiste sur la valeur d'un traitement intensif et de longue durée sous contrôle constant.

Primär vitamin-resistente Rachitis.

Ein typischer Fall eines 8jährigen Mädchens mit primär vitamin-resistenter Rachitis wird besprochen. Während der Behandlung mit grossen Dosen von Vitamin-D wurde das Calcium-Phosphor-Verhältnis positiv und die Rachitis heilte allmählich aus. Angesichts der Tatsache, dass die Krankheit in den letzten Jahren erneutes Interesse gefunden hat, wurden die Probleme der Differentialdiagnose und der Therapie besprochen mit Berücksichtigung des Wertes einer lang fortgesetzten und intensiven Behandlung unter dauernder Kontrolle.

Raquitismo vitamino-resistente primario.

Se refiere el caso de un raquitismo vitamino resistente primario en una niña de ocho años. Durante el tratamiento con grandes dosis de vitamina D el balance calcio y fósforo se tornó positivo y el raquitismo gradualmente curó. Siendo esta enfermedad de renovado interés durante los recentes años, se discute el problema del diagnóstico diferencial y de la terapéutica, con énfasis sobre el valor de un largo, continuado e intensivo tratamiento bajo constante control.

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Section of Pediatrics and School Hygiene of the Swedish Medical Society

Meeting, April 15, 1955

R. Zetterström: **Studies on the etiology of the celiac syndrome.**

The symptoms in idopathic celiac disease are similar to those observed in patients indisposed by marked deficiency of the small intestines. This becomes apparent by comparing the symptoms and clinical findings in a series of children having typical celiac disease with those in a ten-month-old infant, from whom approximately 1 meter of the small intestines was removed at three weeks of age, as well as in a ten-year-old boy with diffuse mesenterial lymphangiomatosis. All these cases showed deficient fat-resorption and marked dysfunction of the small intestines. Other observed signs seem to be secondary to the steathorrhea. The comparison also showed that when typical celiac signs develop in other conditions than in idiopatic celiac disease very grave lesions must exist. This indicates that the functional intestinal disturbance in celiac disease is extremely severe. Since it has been shown that wheat gluten gives rise to a celiac syndrome in children disposed to this disease, this fact lends strength to the opinion that a special type of allergy may be its primary cause. In order to find further support for this theory, the effect has been studied of peroral wheat gluten administration on the histamin concentration in the blood in four children with idiopathic celiac disease, who have been free from symptoms after treatment with gluten-free diet. In all cases a pronounced decrease of the blood histamin was found within 24 hours after its administration, which is the reaction one may expect after administration of an allergen to a sensitized individual. In a case not already treated with gluten-free diet, the histamin concentration was so low that it could not be determined. This study lends support to the theory that gastrointestinal allergy to wheat gluten is the primary etiology of idiopatic celiac disease. The intestinal allergic reaction leads in its turn to severe functional disturbance.

B. Brante, K. Kaijser and E. Ottoson: **Examination of the thyreoid function by means of isotopic iodine in children.**

Ninety-seven children have been tested with a total of 142 isotopic iodine samples. The children belong to all age groups, from prematures to 15 years of age, boys as well as girls. Isotopic iodine was administered perorally in a dose of 1 microcurie per 7 kg body weight to the older children, and $^1/_2$–$^1/_4$ of this dose to newborns and prematures. The measurements were made over the thyreoid gland, in the urine and in the plasma. The findings in the children, perhaps with exception of the newborn period, are identical with those in adults. In 6 prematures the findings varied considerably, due perhaps to variations in the absorption, renal function, and in the state of nutrition. Parenteral

administration of the isotopic iodine was therefore considered better in this group of children. The iodine excretion in the mother's milk was about 10–20 per cent of the given dose. In girls at puberty with struma but without signs of thyreotoxicosis, a marked increased uptake of isotopic iodine in the thyreoidea was found. There was, however, no increased rapidity of the output to the plasma of isotopic iodine containing hormone, which together with normal protein-bound iodine level militates against increased thyreoid hormonal production. A simple 24-hour determination of the urinary excretion of isotopic iodine will therefore be misleading as a test on the thyreoid function in these cases. In assessing obesitas in children the method with isotopic iodine is of value as a complement to other examinations, because the result of these examinations often indicates fallaciously a tendency to hypofunction.

M. d'Avignon: **Pseudohypothyreosis.**

Report of three children, aged 13–20 months, with a retarded mental development corresponding to about I.Q. 30. The development of the bone-centers was considerably retarded. The basal metabolism rate corresponded to that in hypothyreosis. The uptake of I^{131} over the thyreoid gland showed also hypothyreotic values. The protein-bound iodine was normal. In the tolerance test with I^{131} after TSH medication the uptake of iodine was increased. The basal metabolism rate was not influenced by thyreoid treatment. There were no signs of deficient function of thyreoid or pituitary gland. All three children had an evident primary encephalopathy of unknown origin. It is supposed that the disturbance of the metabolism of the thyreoid hormone was due to some cerebral lesion.

R. Stempfel: **Serum and cerebrospinal fluid bilirubin in hemolytic disease of the newborn.**

Kernicterus may occur in conditions other than hemolytic disease of the newborn. It does not occur in the absence of hyperbilirubinemia, however, and it has been satisfactorily demonstrated that the incidence of this complication is roughly proportional to the degree of hyperbilirubinemia. Since the indirect-reacting pigment is the predominant bilirubin fraction in the neonatal period it is felt that indirect bilirubin may be the involved neurotoxin. The relationship between the serum and cerebrospinal fluid bilirubin concentration was studied in 25 infants with hemolytic disease of the newborn. Of the 54 spinal fluid samples examined, measurable amounts of bilirubin were present in all cases. In the presence of a predominantly indirect hyperbilirubinemia, the spinal fluid pigment was predominantly indirectly reacting, which lends support to the contention that indirect bilirubin can and does cross the blood:CSF-barrier. Though a trend to a relationship exists, there was no direct correlation between the serum total bilirubin and the spinal fluid total bilirubin. This finding was supported by spectrophotometric absorption analyses on 13 serum-spinal fluid sample pairs and is an indication of individual variations in blood:CSF-barrier permeability. The spinal fluid total protein values were seen to vary over a wide range, but bore a highly significant correlation ($p < 0.001$) to the spinal fluid indirect bilirubin concentration. This supplies further evidence of blood:CSF-barrier permeability variations. Whether these variations are the result of immaturity alone, or whether they reflect some direct toxic action of indirect bilirubin, cannot be determined from these data. If indirect bilirubin is neurotoxic, however, it is quite probable that the blood:CSF-barrier permeability is a limiting factor in the development of kernicterus.

Jaime Fr. Cereceda: **Case of agenesia corporis callosi with hypertelorism.**

Five-year-old boy. Parents healthy. Pregnancy without comments. Delivery 7 weeks prematurely. The child displayed unsatisfactory physical and psychic development. The circumference of the skull was 42 cm. The large fontanel measured 6 × 5 cm; the distance between the eyes was 40 mm and between the pupils 57 mm. Encephalography showed typical findings of agenesia of the corpus callosum: increased distance between the lateral ventricles, concave medial limits of the lateral ventricles, dilatation of the posterior horn of the lateral ventricles.

Meeting, June 4, 1955

Sture Falkmer and Matts Pehrsson: **Neonatal hepatitis and partial intrahepatic atresia of the bileducts in two siblings.**

Report of a boy that fell ill with progressive jaundice at three weeks of age. The clinical picture was that of biliary duct obstruction. The patient died at seven months of age. Autopsy revealed an atresia of numerous small and medium-large intrahepatic bileducts, together with intralobular stasis and slight chronic peri-cholangiolitic changes. The patient's sister fell ill at three weeks of age with jaundice and presented the same clinical picture. Explorative laparatomy performed at two and a half months of age showed, however, normal extrahepatic bileducts and biopsy of the liver showed no signs of obstruction of the intrahepatic bileducts. There was, however, a marked hepatitis, the microscopic picture of which was dominated by a transformation of parenchyma cells to polynuclear giant cells. The girl is still, at seven month of age, in satisfactory state of health and she has only slight jaundice. The cause of the jaundice in the latter case is unexplained. There was no suspicion of Rh incompatibility or of ABO immunization.

Discussion.—*Erik Frisell* and *C. W. Lundquist.* A boy in good health until five month of age, fell ill with progressive jaundice, and presented bilirubinuria and white-gray stools. Laparotomy was performed at six and a half month of age because of suspicion of biliary duct obstruction. The bileducts were free; there was hepatomegalia with portal lymphadenitis. Postoperative nosocomial infection occurred and after some weeks the child died. At autopsy the liver showed the usual picture of hepatitis with numerous polynuclear liver giant cells. In this case one believed that the hepatitis was due to a virus infection; polynuclear giant livercells may be, however, an expression of a special type of reaction to various stimuli, especially during the first month of life.

Lars Garby: **Some studies regarding the metabolism of human amniotic fluid.**

Freshly isolated amniotic membranes removed from normal deliveries were stretched in a diffusion-chamber with Krebs-Ringer's fluid held at 37°C. In this set-up the transport of water, sodium and chloride was determined by means of isotopes. Since O is the potential of the transmembrane in this system the determined transports express the self-diffusion of the molecules and ions, respectively, passing through the membrane. The exchange rapidities that have been determined by this means are of the same size as those that have been found in *in vivo* studies by Flexner, Cox, Plentl and their coworkers. The author concludes that the exchange of water and electrolytes

determined in *in vivo* experiments simply expresses the self-diffusion through the amnion membrane of the solitary components.

DISCUSSION.—*K. Kaijser.* In order to prevent too rapid decrease of the body weight, premature babies have been put into a diver-like suit filled with Ringer's solution to which protein has been added, or the child has been put in a vessel filled with the same solution.

B. S. Bille: **Hypoproteinemia in diseases of the pancreas.**

Report of a case of familiar pancreatic dysfunction with hypoproteinemia and edema, symptoms of which disappeared after substitution therapy. There was no nutritional protein deficiency nor loss of protein in the urine, or damage of the liver, that could explain the hypoptoteinemia. A resorption deficiency was probably the true cause. In cases of idiopatic hypoproteinemia reported in the current literature often record is made of the function of the pancreas. In these cases one should reckon with the possibility that there might have been a pancreatic dysfunction.

Stig Sjölin: **On the possibilities of differentiation between recent and old red blood corpuscles in samples of cerebrospinal fluid.**

There are two types of stellated red corpuscles. The first type develops rapidly in beginning hemolysis. These corpuscles are characterized by numerous and very fine spikes. The other type is considered to depend upon slowly developing changes of the physical condition of the hemoglobin, producing a jelly formation or a chrystallization. The spikes in this type are fewer and rougher. In diluted solutions with a low protein content and a bad buffer capacity the red corpuscles are very sensitive to hemolytic factors such as hypotonia, pH-changes, fatty-acids and other surface-active substances. A stella-formation due to lysis very easily develops. It has been shown that red corpuscles in the cerebrospinal fluid often become stellated in connection with the lumbar puncture or during examination of the liquor samples. This type of stellation is therefore of no value in the differentiation between intracranial bleeding and accidental bleeding at the lumbar puncture. The existence of hemolysed red corpuscles, so-called ghost-cells, in a liquor-sample indicates on the other hand that the red corpuscles derive from an intracranial bleeding.

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ANNOUNCEMENTS

VIII International Congress of Paediatrics, Copenhagen, July 22—27, 1956

The scientific programme comprises plenary sessions, round-table conferences, sectional meetings, and an exhibition. At the plenary sessions the following lectures will be held:

Monday, July 23rd:

I. *Prenatal Injuries and Malformations*

1. Genetic injuries from irradiation (atomic bomb).
2. Prenatal infections.
3. Prenatal prophylaxis.

II. *Chemical Agents*

1. Fluoridated water in the prevention of dental caries.
2. Dangers involved in the use of antibiotics.
3. Dangers from industrially manufactured foods.

Tuesday, July 24th:

I. *Pathology of the Newborn: Anoxia*

1. Mechanism of anoxia.
2. Pathological anatomy of anoxia.
3. Oxygen therapy—value and risks.

II. *Surgery*

1. Malignant diseases in childhood.
2. Urological problems.
3. Late results of operation for cyanotic heart diseases.

Wednesday, July 25th:

I. *Child Psychiatry*

1. Neuroses in childhood.
2. Prevention of accidents.
3. Early diagnosis of mental deficiency.

II. *Neurology*

1. Hydrocephalus.
2. Cerebral palsy—results of long-term physiotherapy.
3. Kernicterus.

Thursday, July 26lh:

I. *Infections*
   1. Vaccination against poliomyelitis.

II. *Allergy*
   1. Bacterial allergy: Diagnosis and incidence.
   2. Bacterial allergy: Treatment and results.

Friday, July 27th:

I. *Problems in Tropical Paediatrics*
   1. Kwashiorkor.
   2. Chagas' Disease.
   3. Ascariasis.

II. *Tuberculosis*
   1. Prophylaxis of tuberculosis.
   2. Treatment of primary tuberculosis.
   3. Treatment of tuberculous meningitis.

Proffered papers will be read in sectional meetings.

It is also planned to arrange round-table conferences with the following subjects:

1. Auricular septal defect.
2. Epilepsy.
3. Leukaemia.
4. Haemophilia.
5. Amino acid metabolism.
6. Nephrosis.
7. Water and electrolyte metabolism in dehydration.
8. The adreno-genital syndrome.

Films of paediatric interest will be shown in the Congress Cinema.

A scientific and technical exhibition will be arranged in connection with the Congress.

The preliminary programme will be sent out in a few weeks.

For further information please apply to:

VIII International Congress of Paediatrics, Domus Medica,
12 A Kristianiagade, Copenhagen Ø, Denmark.

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